EMERGING TECHNOLOGIES AND THEIR IMPACT
March/April 2006
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Technology Review

AN MIT ENTERPRISE

ANNUAL REPORT

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The Knowledge

Advances in biotechnology have put bioweapons within the reach of terrorists and offer governments new opportunities for violence and repression.

BY MARK WILLIAMS

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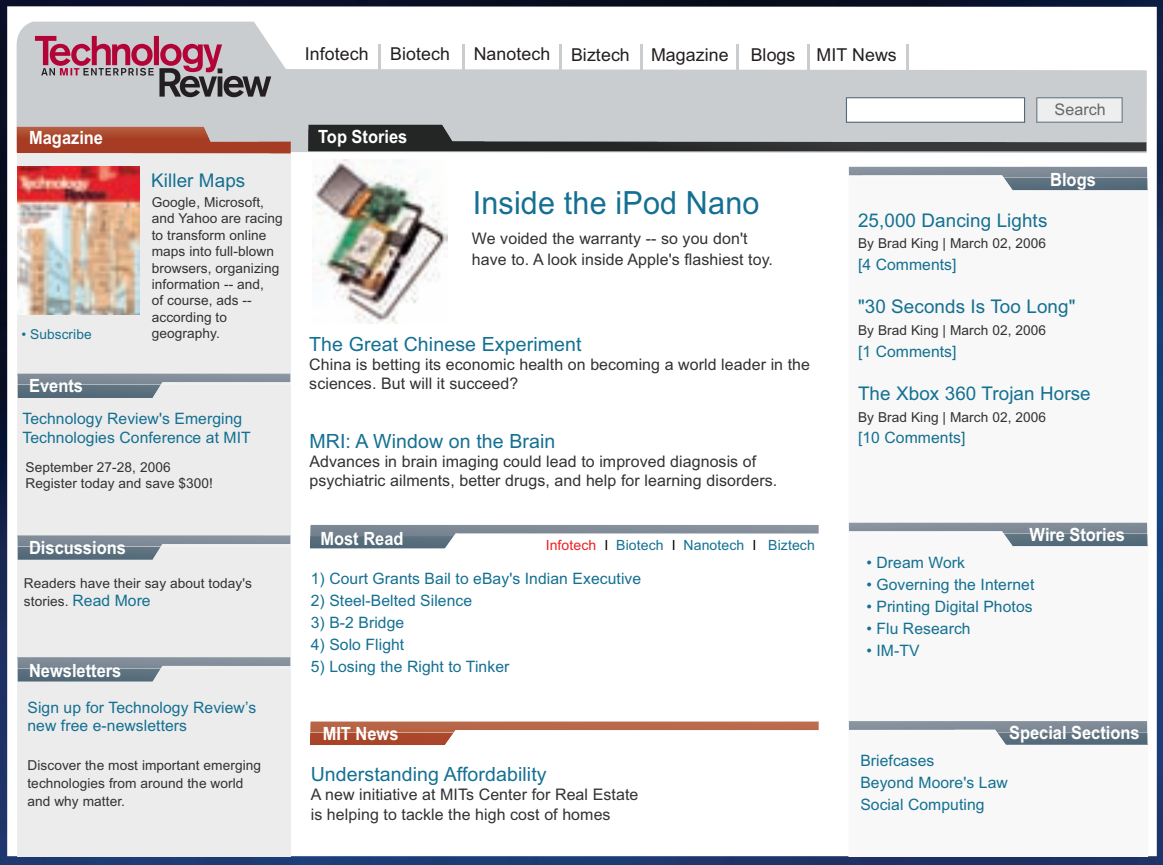

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Contributors

Mark Williams wrote this month's cover story *(see "The Knowledge," p. 44)*, which recounts research that was done by the former Soviet Union's 30,000-worker bioweapons program, and which assesses how much today's molecular biology might enable that work to be duplicated in small laboratories. "With its capability to reframe the terms of life itself, biotechnology is more powerful than any technology that's preceded it in human history," says Williams, who also wrote this month's review of NASA's push to privatize some functions of the United States' manned spaceflight efforts *(see "Private Space," p. 80)*.

Erika Jonietz was the guest editor of this year's list of breakthroughs *(see "10 Emerging Technologies," p. 55)*. "Trying to pick 10 technologies that are cutting edge *and* likely to stand the test of time is daunting," she says. "You almost never find consensus about a topic's importance—especially when reaching into fields, such as stem-cell research, that are both frontier science and politically charged. I just hope we found interesting people doing exciting research." After 11 years in Boston, including four earning a degree from MIT and three as an editor at *Technology Review*, Jonietz returned to her native Texas to pursue a freelance-writing and editing career in 2003.

Kamil Vojnar did the artwork for this month's cover—and is the man pictured in the biosuit. "The damn thing was heavy," he reports. "At first I thought I would never be able to get myself inside and would have to politely excuse myself from the project." Vojnar was born in Czechoslovakia, studied at the Art Institute of Philadelphia, spent a few years in New York, and is currently a freelancer based in France, where, he says, "the croissants are better. But I surely miss my bagels." Vojnar's work has appeared in a variety of publications, including the *Atlantic Monthly*, *Life*, and *Scientific American*.

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The Loss of Biological Innocence

Advances in biotech present dark possibilities and an editor's dilemma.

When, if ever, should editors *not* publish a story they think is true, but they know is controversial? Well, if publication is dangerous or useless. That question was suggested by this month's cover story by contributing writer Mark Williams *(see "The Knowledge," p. 44)*.

Williams (for the record, my brother) spent 14 months investigating genetically engineered biological weapons. He immersed himself in their arcane biology, and he interviewed numerous scientists and security experts. But his journalistic coup was securing the candor of Serguei Popov, a former Soviet bioweaponeer.

Popov described how Biopreparat, the Soviet agency that secretly developed bioweapons during the Cold War, created recombinant pathogens that produced novel symptoms. Some of those symptoms were very horrible. In one case, Popov and his researchers spliced mammalian DNA that expressed fragments of myelin protein, the insulating layer that sheathes our neurons, into *Legionella pneumophila*, a bacterium responsible for pneumonia. In Williams's account, "In test animals…the myelin fragments borne by the recombinant Legionella goaded the animals' immune systems to read their own natural myelin as pathogenic and to attack it. Brain damage, paralysis, and nearly 100 percent mortality resulted." But Biopreparat had more expansive ambitions than poisoning populations. The military scientists who ran the agency wanted bioweapons that could alter behavior, and they investigated using pathogens to induce memory loss, depression, or fear.

This information might be of only sinister, nostalgic interest, but for Williams's thesis. He argues that the advance of biotechnology—in particular, the technology to synthesize ever larger DNA sequences—means that "at least some of what the Soviet bioweaponeers did with difficulty and expense can now be done easily and cheaply. And *all* of what they accomplished can be duplicated with time and money." Williams explains how gene-sequencing equipment bought secondhand on eBay, and unregulated biological material delivered in a FedEx package, can be misused. He concludes that terrorists could create simple weapons like Popov's myelin autoimmunity weapon, and states could engineer the more ambitious recombinant pathogens that Biopreparat contemplated.

All of this is tremendously controversial. Critics within the U.S. defense community dismiss Popov's accounts of what Biopreparat achieved. Most security experts believe that creating any bioweapon—let alone a recombinant pathogen—is difficult, and "weaponizing" those agents is nearly impossible. And many biologists, whilst not as sanguine about the difficulties, think that a preoccupation with bioweapons is counterproductive for two reasons: first, because funding biodefense research tends to disseminate knowledge of how to develop such weapons; second, because we don't have a very good idea of how to defend ourselves against them.

When I quizzed people involved with national security, they warned me off publishing. Our story might give our enemies ideas, they said. If we had no recommendations for improving public safety, we had better kill the piece.

These arguments have weight. Therefore, why publish? We had encouragement. Distinguished scientists who are familiar with bioweapons, including George Poste, the former chief scientist at SmithKline Beecham and the sometime chairman of a task force on bioterrorism at the U.S. Defense Department, were supportive. The scientists confirmed that the advance of biological knowledge offered malefactors new categories of weapons with new opportunities for violence and coercion. As Poste told me, "Biology is losing its innocence. For a long time, biology was irrelevant to national security. But that's changing. The biological revolution means a determined actor can undoubtedly build a biological weapon." Additionally, in February a long report by the Institute of Medicine and National Research Council of the National Academies entitled "Globalization, Biosecurity, and the Future of the Life Sciences" provided us moral support. It replicated much of our reporting and conclusions, and while we were sorry to be scooped, we were relieved to be in such respectable company.

Nevertheless, we took a number of precautions. We were careful to occlude any recipes for bioweapons. What detail we do provide is based on published research and has been widely discussed. Finally, in the interests of balance, we asked Allison Macfarlane, a senior research associate in the Technology Group of MIT's Security Studies Program, to rebut our argument *(see "Assessing the Threat," p. 34)*.

Yet, in the end, we published the story because we believed it was important. Modern biotechnology is potentially a threat to our welfare, but the life sciences will continue to advance. Thus, our best hope of countering the threat is to invest in research that will suggest a technological solution. But as Serguei Popov himself told us, "First we have to be aware." Write to me at jason.pontin@technologyreview.com. **Jason Pontin**

MARK OSTOW

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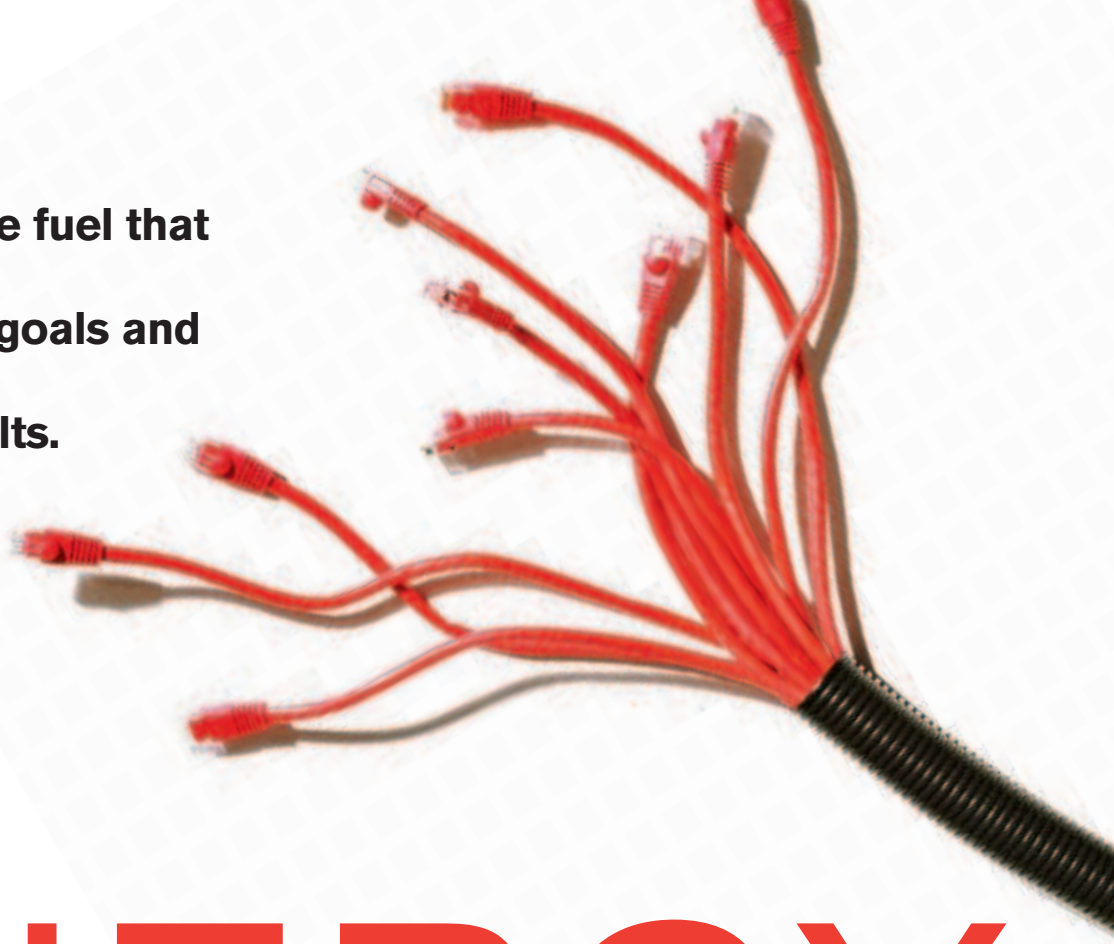

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Letters

The State of the Internet

David Clark's approach to the problems of the Internet ("The Internet Is Broken," December 2005/January 2006), to redesign its infrastructure, bears a similarity to the medical profession's approach in the 1960s and '70s to the "bubble boy" syndrome (severe combined immunodeficiency, or SCID). Both are attempts to sterilize the environment so that the immune-deficient subject can survive. It did not work then for those patients, and it won't work now for the Internet's security.

The medical profession today takes care of SCID patients by giving them new immune systems through bone marrow transplants. We should be looking to do the same for our data, so it can travel throughout the existing Internet infrastructure.

Frank J. Sauer
Arlington, VA

While I fully support the optimization of the Internet, creating a worldwide tracking infrastructure that people can't opt out of will only ensure that governments can keep information from reaching their people, quashing dissent.

Also, adding complexity to routers and other infrastructure devices will only ensure that more vulnerabilities in the additional code will expose even more devices to malware attacks and slow down our communications.

Finally, the end point should be designed for the security it requires. The Internet shouldn't be the primary source of user security; the host devices should.

Corinne Cook
Denver, CO

David Talbot's Internet story is, of course, right on. But as I read it, I could not help editing it in my mind, substituting the term "Microsoft Windows" wherever "the Internet" appeared.

Unfortunately, the ubiquity of highly vulnerable Windows has left a good part of the world at a risk that's perhaps almost as dangerous and widespread as the risk posed by a broken Internet. Many of the observations about the Internet made by Clark and Talbot would apply just as well to Windows. I hope someone will soon detail that exposure.

David Munroe
Montgomery, OH

Science in China

Horace Freeland Judson doesn't heed his own admonition at the beginning of "The Great Chinese Experiment" (December 2005/January 2006). He acknowledges that "even sophisticated and knowledgeable Westerners bring ideological preconceptions to their view of China" and rightly points out that Westerners have often made the erroneous assumption that laissez-faire capitalism "will inevitably lead to democratic reforms." For the last 15 years, China has had a booming economy but practices neither capitalism nor democracy as we understand it.

But then Mr. Judson spends much of his article explaining how the Chinese science ethos, with its attachment to what he calls a "Confucian" respect for elders and seniority, discourages the development of a questioning culture, a barrier to good science. But to the degree that Chinese scientists follow Confucian practices, these practices are not strictly about scientific method and what Chinese scientists actually do in the lab. It is clear to me—a China watcher even before my MIT days—that China is finding its own route to scientific success, just as it found its own path to economic growth.

Lisa A. Suits
Bethesda, MD

The realization that China needed to change in response to Western encroachment dates no later than 1842, when China lost humiliatingly in a war against the British Empire over the issue of British sale of opium in China. Then, as now, China was guided by a myth: that the key to a modern China is simply science and technology.

One notable attack on that myth was the cry for democracy and science made during the May 4 student uprising of 1919. Many founding fathers of the Chinese Communist Party, which later founded the People's Republic of China in 1949 (the current China as we know it), were among the leaders of that uprising. Unfortunately, since then, most Chinese politicians seem to have forgotten the foresight and the causes of their forefathers.

Wang-Ping Chen
Champaign, IL

Changes at *Technology Review*

From the December 2005/January 2006 issue: "*Technology Review* has been a print magazine with a website; from now on, we will be an electronic publisher that also prints a magazine." That same issue's cover reads, "The Internet Is Broken." Such masterful use of irony deserves an award!

Art Goddard
Costa Mesa, CA

The editor responds:
Thank you, but we're sure we don't deserve one. We reported on shortcomings of the Internet as it is now constituted, and we described various proposals to fix them. We are confident they will succeed and that the future Technology Review *will happily exist on a reconstituted Internet.*

Correction: The caption on page 48 of the December 2005/January 2006 photo essay "Dirty Oil" should have read "roughly 30 cubic meters of natural gas per barrel of recovered oil," not "roughly 300 cubic meters."

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Canary Islands Coastline

Desalination in Spain

By Cynthia Graber

Spain built Europe's first desalination plant nearly 40 years ago and is the largest user of desalination technology in the Western world. Spanish companies lead the market, operating in regions including India, the Middle East, and North America. Spanish innovation contributes to advancing desalination to bring sustainable clean water to millions.This is the second in an eight-part series highlighting new technologies in Spain and is produced by Technology Review, Inc.'s custom-publishing division in partnership with the Trade Commission of Spain.

Just steps away from the Mediterranean sea along Spain's southern coast, machinery hums inside Carboneras, Europe's largest seawater desalination plant. Throughout the building, water flows through brightly colored pipes and tanks, along the way passing through layers of chemical and physical filtration before the seawater reaches the heart of the plant, the reverse-osmosis membranes that turn saltwater into fresh. This plant is the latest marker in Spain's decades of experience and research in the field of desalination. It represents the efforts of some of the top Spanish firms in the field, both in Spain and around the world.

For the past nearly 40 years, companies in Spain have built and operated desalination plants, first in the water-poor Canary Islands off the coast of Africa, then moving to fulfill water needs on the Spanish mainland and around the world. These companies, and the companies that provide a wide variety of parts for desalination plants, have grown, constantly honing and improving both cost and efficiency. Research continues in the Canary Islands for ways to couple desalination with renewable energy to provide sustainable, ecological solutions for communities in developing countries. Today, Spanish companies make up the largest percentage of competitors on the international market for the design, engineering, construction, and operation of new desalination plants around the world.

History of Desalination

The idea that pure water could be made from seawater has been tantalizing thirsty humans for hundreds, if not thousands, of years. The original premise was based on the idea that boiling or evaporating water separates the water from the salt. That theory—vaporization or distillation—was behind the technol-

ogy for the first large-scale desalination plants that sprouted in desert areas in the 1950s and 1960s, primarily in the Middle East. These areas, lacking water but with plenty of fuel to burn, turned one resource, energy, into what the region craved: water. The technologies using heat, though, require vast amounts of energy.

Researchers throughout the early 1900s had been studying the idea of using a membrane to separate out salt from seawater. This is based on the osmotic nature of cell walls: certain semipermeable membranes, such as animal and plant cell walls, allow water to pass through, creating an equilibrium between a highly concentrated solution on one side of the membrane and a diluted concentration on the other.

Scientists hypothesized that with the right amount of pressure and with the correct membrane design, this natural phenomenon could be reversed through a man-made membrane. Instead of flowing from a diluted solution to a highly concentrated one, equalizing them both, the concentrate could be forced through a membrane, leaving an even higher concentrated solution of dissolved solids (in this case, salt) behind.

In the 1960s, researchers in the U.S. and Japan who developed membranes for industrial purposes soon realized that those same semipermeable man-made membranes could be used in desalination. By the 1970s, desalination-plant developers adopted reverse osmosis (RO) for use in new desalination plants.

Though more efficient than vaporization or distillation and requiring far less physical space for the same operation, these plants still demanded a high energy input. Over time, engineers developed recovery systems to take advantage of the high pressure of waste brine left after the reverse-osmosis process. This has led to precipitous drops in energy needs for the process, reducing the cost, while the cost of the membranes used in reverse-osmosis technology have also dropped about 50 percent.

At the same time, conventional sources of fresh water have proven more costly in recent years. In some areas, coastal aquifers are depleted of water before they can refill naturally, leading to the intrusion of seawater. All these factors contribute to the fact that, in some regions, desalination has become cost-competitive with traditional methods of supplying water needs.

Today, there are more than 15,000 desalination plants in the world.

Why Spain?

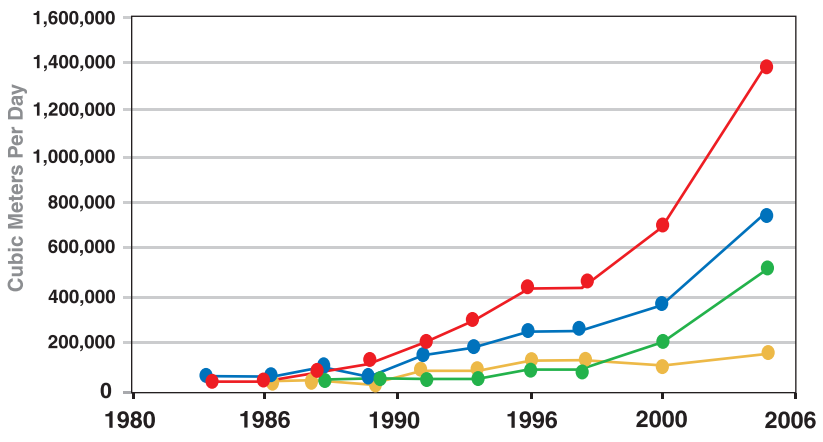
Spain provided the home for Europe's entrance into the desalination industry with the first plant installed on the island of Lanzarote in the Canary Islands in 1964. Since then, the process has expanded throughout the islands and on the Spanish mainland as well. Today, Spain is the fourth-largest user of desalination technology in the world, behind Saudi Arabia, the United Arab Emirates, and Kuwait. Spain's more than 700 plants produce approximately 1,600,000 cubic meters of water each day, or enough for about 8 million inhabitants.

The Canary Islands aren't the only dry areas of the country in need of new water sources. The coast along the Mediterranean, particularly in the south, has long suffered periods of droughts and inadequate access to water. Despite water scarcity, the sun and climate have made the southern region the agricultural breadbasket of Spain and of much of Europe, with miles of greenhouses stretching out to the horizon. At the same time, the population in these areas has grown dramatically.

Spain is already the second most visited country in the world, and tourism in Spain is on the rise. In the past decade the south of Spain has increasingly become a destination for retired northern Europeans looking to create a new home in a land with plenty of sun. The local governments have encouraged this type of development, building new homes along with the services necessary for this retired population, such as golf courses. In fact, Spain built a record-breaking 800,000 new properties in 2005, most concentrated along the southern coast; that figure is higher than the combined new properties built in France, Germany, and the U.K.

"Here we encounter the paradox: because of the climate and the long hours of sun, there's a great deal of tourism and very productive agriculture. And yet precisely because of the wonderful climate, there's little water," says Claudio Klynhout, director of communications for AcuaMed, the arm of the Spanish government in charge of the water program.

Use of Desalinated Water in Spain



Total Production
Urban Usage
Agricultural Usage
Industrial Usage

The production of desalinated water in Spain doubled from 2000 to 2004. The Spanish government predicts that production will double again in another five years.

Source: AEDYR

The government has long been a supporter of desalination as a method of dealing with water scarcity. After the Spanish Civil War, Spain's economy was in desperate need of revitalization. The government saw an opportunity to boost economic activities through tourism to the sun-drenched Canary Islands, but the region lacked natural water resources, particularly on the eastern islands. In order to lay the groundwork for economic growth, the government decided to build Europe's first desalination plant in the Canaries. This original plant used the same technology as those in the Middle East, that of vaporization of water. Within a few years, though, the government switched and began using the then-novel reverse-osmosis technology for newer plants.

Recent events have conspired to continue this desalination trend within Spain. Under the past government, officials in Spain had created plans to divert the Ebro River in the water-rich north more than 480 kilometers south to supply the parched regions along the southern coast.

Based on a planned increase in water, developers had rallied behind development schemes costing billions of dollars to build vast tourism complexes between Alicante and Almeria in the south, including dozens of golf courses. But farmers and environmentalists protested that the diversion would have a serious environmental impact on the Ebro and its delta, on the farmland in the north, and along the hundreds of miles of planned pipeline.

When the new government took power in 2004, they put the expected plan on hold. Instead, they've drawn a new plan that supplies water to the south without taking it from the north. The main method involves building 20 new desalination plants all along the Mediterranean coast where needs are highest, focusing on the region in the south. The desalination plants are expected to fulfill 50 percent of the need, with reuse of treated water, increased irrigation efficiency, and other efforts supplying the rest.

"The current government thought that this new plan would be much more secure in guaranteeing water, rain or no rain, independent of the climate," says Klynhout. "In 2005 there was a drought, and there was doubt that the Ebro River would even have had enough water to supply had the planned pipeline been built."

High-pressure pumps push sea water through reverse osmosis membranes housed in narrow blue tubes. Above, desalinated water is stored in tanks to flush seawater at shutdown.

Bidding on the first six of the plants begins in the spring of 2006, with all plants intended for completion by the end of 2008. When operational, these plants will more than double Spain's desalination capacity.

Spanish Companies

The announcement of the plans to develop these new desalination plants within Spain has been a boon for desalination companies. Most also specialize in other forms of water treatment, such as wastewater treatment or water purification. But the real prize for many of these companies, the way they have been able to become significant players on the international market, has been their experience with desalination.

"We have been working for the past 30 years on all these desalination plants," says Jose Antonio Medina, president of the International Desalination Association and head of the Spanish Desalination and Reutilization Association. "That gave Spanish companies the necessary experience with both building and operating plants. At the moment Spain has the highest number of companies in the world with this level of technology and experi-

ence in desalination."

These companies include such names as Pridesa, Inima, Befesa, Cadagua, Sadyt, Infilco, Aqualia, Cobra, Grupo Seta, and IsoluxCorsan Corvian. Degremont, a French multinational company, has a strong desalination sector made up almost entirely of Spaniards.

Nearly all of these companies got their feet wet in the waters off the coast of the Canary Islands. In the portfolio that companies put forth to show their skill and experience, many point to one of the many ground-breaking plants on the Canary Islands. One plant was the first in Europe, another the first large-scale RO plant in Europe, another the first in Europe to take advantage of a new desalination membrane, still another the first to use new energy recovery systems to dramatically reduce energy needs.

"One of the early plants, it was a very complicated plant to operate," says Medina. "I worked at that plant from the beginning. It has been like the university of reverse osmosis for us."

At times today the companies are competitors when submitting bids for new plants, whether for individual stages, such as the design, or for the plant's building and operation. At times the companies work in various consortia. The Spanish government, in an effort to support a variety of Spanish companies, divided the development of the landmark Carboneras plant. Separate bids were taken for the design and engineering, construction, and operation of the plant. At the end, Inima worked out the engineering and design details. A consortium of Pridesa, Degremont, Befesa, and OHL, Inima's parent company, undertook the construction. Today, Inima operates the plant.

This experience with different aspects of plant development and management and with a wide variety of plants is the key to the companies' competitiveness, according to representatives. "Each plant is different," says Ignacio Zuñiga, international business development manager of Cadagua. "There are different conditions in different oceans. And the conditions of the intake of the plant or the level of pollution in the area, all of these affect the pretreatment of the water and the design of the entire plant."

Representatives of each company, in competing against the others in the market, point to specific company strengths. Most are backed by large construction groups or other financially secure, multinational companies that provide the needed resources and stability for investments in this sector. All have years of experience working in Spain.

Officials at Befesa, part of the Abengoa Group, say one key to their advantage has been their willingness to take a chance in newer, financially riskier markets around the word. Befesa was one of the first Spanish companies operating in Algeria and is now building the first desalination plant in India.

"This is our philosophy–when we start work in a country, we do so because we have a strategy to be working in that country," says Guillermo Bravo, CEO of Befesa. "We now have three plants in Algeria, and we plan to develop the market in India."

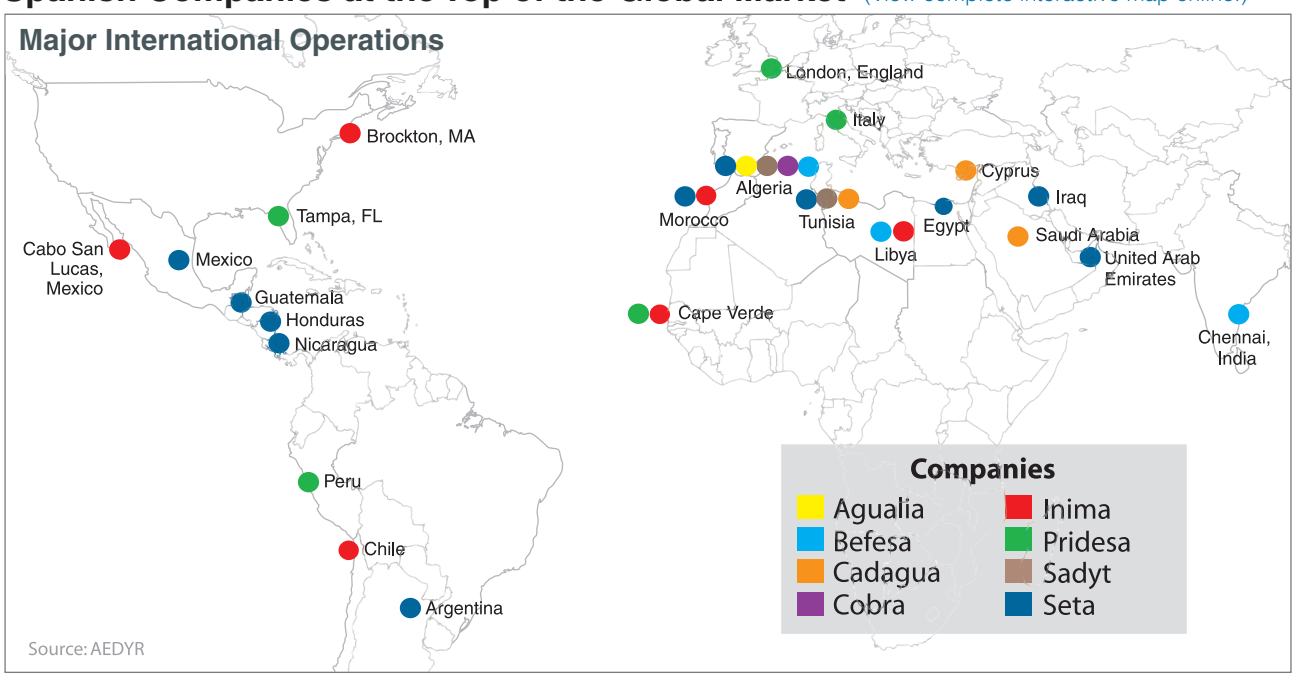
Befesa is also conducting research on the possibility of reusing desalination membranes for other purposes after replacement, thus reducing the overall cost of the facility.

Inima, which has dozens of desalination plants in Spain and around the world, points to their decades of experience, the financial backing of the international construction company OHL, and their ability to work in all aspects of water treatment.

Not only are Spanish companies building new plants, but in the U.S. one Spanish firm is attempting to fix an existing plant. The Tampa Bay Seawater Desalination Plant, the first large Ameri-

Spanish Companies at the Top of the Global Market

(View complete interactive map online.)



can seawater desalination plant, originally begun in 1999, has been inundated with problems from the beginning, due in part to challenges with construction, management, and pretreatment of the seawater. Pridesa, a Spanish company now owned by RWE Thames Water, won a contract, in partnership with American Water, to take over the plant.

Jose Maria Ortega, international commercial director of Pridesa, admits that rehabilitating an existing plant is much more challenging than building one from scratch. "We thought it was a huge opportunity to set up a good precedent for seawater desalination in the American market," says Ortega, "with ourselves as the main protagonist."

Supporting Companies

The membranes used in most Spanish desalination plants are the heart of the desalination plant. They are produced primarily by American and Japanese companies, though some institutions in Spain have begun undertaking research into membrane production. Spanish companies, however, have developed the parts to fill many of the needs in these large-scale plants around the world. The Spanish Desalination and Reutilization Association counts nearly 60 companies as members, all involved in some aspect of desalination, from producing filters and valves to the large companies that build the plants.

Along the northern coast of Spain, the land is lush and green, a visual contrast to the parched areas of the south. The cities and towns around the industrial city of Bilbao form Spain's most concentrated industrial corridor, with a large number of metal foundries and manufacturing plants.

Though this area can provide for it's water needs without desalination technology, nevertheless a number of companies have specialized in meeting the needs of desalination. Desalinating seawater involves particular engineering challenges, including dealing with the high corrosivity of the water and the extremely high pressure needed to force the water through the membrane.

High-pressure plug valves await shipping at an MTS Valves warehouse in the north of Spain.

One of the companies in the north, MTS Valves, makes high-pressure valves for all sorts of mechanical needs. As the desalination industry grew, it began developing the needed valves, then specialized in the valves of the noncorrosive alloys of stainless steel called duplex and superduplex that are very expensive and difficult to cast. The fact that there are two foundries in the Bilbao region that work with this metal has proven to be a boon for local companies.

Says Jose Ignacio de la Fuente, factory manager of MTS Valves, "We have been in this market for more than 30 years. We are the European leaders in this market, supplying valves to plants around the world, to Israel, Singapore, Australia, the United Arab Emirates, and Algeria. We are in the position to guarantee a first-class product by working with our suppliers." De la Fuente says MTS Valves continues to research ways to optimize the performance of the valves, aiding in reducing the overall cost of water production.

Indar Maquinas Hidraulicas (Indar Hydraulic Machines) has also been able to take advantage of the local availability of duplex and superduplex alloys to create submersible motors and high-pressure hydraulic pumps for the intake of seawater from beach wells or intake tanks. Originally a family-owned business that began in 1940 manufacturing small motors for area companies, the company began to focus on submersible motors and pumps when desalination began in Spain in the 1960s.

As the market developed, Indar continued making pumps for other water-treatment plants while honing its desalination niche by working with these challenging alloys. Taking it one step further, Indar have now created an even more specialized niche by focusing on pumps and engines of larger diameter, suitable for the newer large desalination plants. Recent research has led the company to develop a pump and motor that saves enough energy to recoup the cost of the new pump in only one year.

"We design the systems to stay competitive, to reduce power consumption as much as possible," says Marcos Garcia, sales manager of Indar.

In desalination, a crucial factor is pre-

treatment, cleaning the water to the highest level possible before it reaches the reverse-osmosis membranes, the most important, expensive, and delicate part of the entire operation. The purer the water, the longer the membranes last and the more effective they remain.

Fluytec, a company based near Bilbao, creates filter systems for the second level of treatment in a desalination plant. Its filters, which look like long cylinders of wound yarn, are cased inside a cylindrical housing. To innovate and distinguish itsselve in this market, Fluytec has developed a method of building the casing out of noncorrosive fiberglass-reinforced plastic (FRP), which unlike PVC can withstand high-water pressures at much larger sizes. In the case of large-scale plants, the FRP filters must be laid out and layered by hand, a task that few companies are able to accomplish.

In addition, Fluytec has developed a new system for replacing filters in extremely large plants, mechanizing the process whereby filters are cleaned or replaced. "In the past it was done by hand. With this new system, filters will be offduty for only a short time," says Jorge Merlo, in charge of international sales for Fluytec.

Dozens of other Spanish companies have developed expertise in niche markets in desalination, marketing their products within Spain and around the world.

Environmental Challenges

When countries or municipalities propose new desalination plants, concerns about the environmental effects often arise in terms of energy consumption and the disposal of the residual brine. For every liter of water taken from the sea, less than half becomes desalted. The remaining brine has about twice the salinity of seawater and is usually returned to the sea.

"The brine could be a problem in theory, but it usually isn't," says Medina. "You have to study how resistant the marine life is to different levels of salinity, and you have to study the conditions of the sea in that area."

The effects of the brine on the surrounding flora and fauna in the sea depend on the specific marine life in the disposal area. The usual response is to pipe the outflow far enough from sensitive species that the water quickly disperses into the surroundings. This is carefully considered in all plans for new plants, and despite extensive research, there has not been a documented case of serious deleterious effect resulting from the disposal of brine.

At the same time, companies are aware of the need to mitigate the effect of brine on the surrounding seabed. Before the development of a plant begins, careful studies are done on the sensitivity of the local marine life. Various techniques to diffuse the brine may be employed. At times, desalination plants are built close to power plants, as is the case with the Carboneras plant. The brine from Carboneras is mixed with the cooling water of the thermal power plant, diluting the brine to a percentage closer to that of the original seawater. Another option is to build a plant close to a wastewater treatment plant; many coastal treatment plants dispose of the residual freshwater directly into the sea, and the two may be mixed together.

"Many people think that desalination has sort of bad impact on the environment. This is exactly the contrary," says Corrado Sommariva, president of the European Desalination Society and divisional director of Mott Macdonald. "Because for instance one of the reasons for selecting desalination in Spain and in Australia was the preservation of some of the existing natural resources which would have been basically depleted if water transmission was implemented instead."

One of the main challenges that remains with the desalination process is the cost of the energy required to produce freshwater. Though different processes demand varying amounts of energy (desalting seawater with membranes requires the most, as it takes tremendous pressure to push the water through the membrane), it remains an issue in terms of cost and environmental issues, as nations around the world battle rising greenhouse gas emissions, such as those emitted by power stations.

In the last 30 years, the amount of energy required for desalination has fallen precipitously, and along with it the price. Decades ago it took approximately 12 kilowatt-hours of energy to produce one cubic meter of freshwater using RO technology; today it takes on average between 3 and 4 kilowatt-hours of energy. Even today, however, the cost of that energy makes up about 40 percent of the total cost to produce each cubic meter of water.

"We design the systems to stay competitive, to reduce power consumption as much as possible," says Marcos Garcia of Indar.

"We are very close to the minimum energy for desalination," says Juan Maria Galtés, director of special projects for Inima. "There's a point where it's impossible to go any further," because of the high pressure needed to separate salt from water.

Developments in new kinds of membranes or other tweaks in plant efficiency could help engineers continue to shave off small amounts of energy, reducing both the cost and the environmental impact.

Canary Islands Renewable Energy

Researching methods to reduce energy use has long been a focus of the Canary Islands Institute of Technology (ITC), a research facility supported by the regional government of the Canary Islands. And scientists there are taking this one step further: they are investigating how to produce freshwater from saltwater without using fossil fuels at all.

"Here, we have a great deal of sun, wind, and seawater. It is an excellent place to develop systems," said Gonzalo Piernavieja, ITC energy and water director. "It is also an ideal place to simulate conditions in many developing countries."

The engineering involved in using renewable energy to power a desalination plant can be relatively simple: solar or wind generators can be hooked up to an

At the Canary Islands Institute of Technology, solar panels feed energy to a stand-alone reverse-osmosis desalination system in operation since 1998. The domes cover desalination prototypes, including workshops and labs.

existing utility grid, which then offsets the power demands of the desalination plant.

The challenge, however, in coupling desalination directly with renewable energy such as solar or wind power lies in the variability of renewable energy. The membranes used in reverse osmosis need to be kept wet, and the systems that make up a desalination plant have been developed to handle a steady stream of water. Solar energy is plentiful when the sun shines and wind power only when the wind blows.

Researchers in the Canary Islands have spent the past decade developing stand-alone small plants that could provide water for approximately 100 to 300 families, about the size of a small village in a developing country. ITC projects are also carried out in conjunction with other international research institutes or companies.

On one Canary Island test site, photovoltaic panels are hooked up to a battery, which feeds a steady supply of electricity to a small desalination plant. "But batteries aren't great because you have to replace them after, say, five or 10 years, and then you have to dispose of them as well," says Piernavieja. "It's better to develop a system that needs no batteries in the first place."

Other solutions tested at the Canary Islands site make use of wind power. In one, a small wind-energy converter powers a seawater RO plant designed to operate even with the stops and starts of wind power. In another, a small wind farm creates a small stand-alone electricity grid that then feeds electricity to the desalination plant.

The Canary island of El Hierro, which has 10,000 inhabitants, hopes to model the future of island living. ITC is involved in a project there in which eventually 100 percent of the island's energy needs will be served by renewable energy; that energy, through a grid, will also power desalination plants that supply all the island's drinking water and irrigation needs.

The ITC research group is one of only a handful focusing on developing and testing plants in which wind turbines directly power the desalination process without going through any grid.

Though all of these systems could be used in industrialized countries, the main goal of the ITC is to develop plants that could theoretically supply water to even a fraction of the billion people around the world in need of clean drinking water. "Many of these people live in areas that have abundant renewable energy resources and yet no electricity grid, and they may never be connected to a grid. This is the philosophy behind our research," says Piernavieja.

ITC research on coupling desalination with renewable energy is already being tested in the world outside the Canary Islands. The ITC has placed four small desalination plants among a population of African fishermen living within the boundaries of a national park called Banc D'Arguin in Mauritania. In 2006, the diesel-run desalination plants are being

converted to run using a hybrid of wind, solar, and diesel power. Wind–solar RO plants are being installed in Morocco, and a solar plant is destined for Tunisia.

Still, these types of applications have many hurdles to overcome. Says Medina, "These types of systems need maintenance. If you install such plants in such a remote place, and if the plants break down, it could take months until someone can be sent there to fix them."

There are applications for these types of stand-alone plants in industrialized countries as well. The ITC is in discussion with the engineering company MTorres, based in northern Spain, about combining the technology developed in the Canary Islands with the ones MTorres is developing: offshore desalination plants powered by wind. MTorres, with extensive experience in wind power, has plans to connect the two fields.

Growth of Desalination

Without a doubt, the use of desalination is rising around the world. The planned new projects in Spain expand the market for Spanish companies. In Algeria, the government, like the Spanish government in the 1960s, is currently acting on the belief that the best way to jump-start the economy is to provide water for private consumption and for industry. To fulfill those needs, Algeria is in the process of building seven large desalination plants. Of those, one will be built by Ionics, a U.S. company owned by General Electric, and one by a Spanish-Canadian consortium. The remaining five will be built entirely by Spanish companies.

Many in the field believe that the U.S., which is plagued by water supply problems in California and Texas, is another emerging market. A number of water districts in California are already in the planning stages for desalination plants along the coast, and Spanish companies are eyeing the state as a center of future business operations. A number of municipalities in Texas are investigating the option of producing potable water from desalination. Inima is already building its first plant in the U.S., a facility near Boston. If Pridesa succeeds in rehabilitating the plant in Tampa, or any other of these newer plants succeeds, it could lead to the development of others.

Mexico is installing its first large-scale desalination plant in the resort town of Los Cabos at the southern tip of Baja California, to be built and operated by Inima. India's Chennai plant, to be built and operated by Befesa, opens the market there, while many Spanish companies are already in talks with the Chinese government about plans for desalination plants. According to Medina, Libya will soon be opening up for bids on desalination plants as well. Israel recently began operating a large RO plant, and Spanish firms are in the competition to build the second one, currently in the planning stages.

In the Middle East, most plants in the past have made use of vaporization technologies, while Spanish companies excel in energy-efficient RO plants. But many new plants in the region are now being installed with RO or hybrid technologies as the price of oil continues to rise. Spanish companies are already working in Saudia Arabia, Oman, and the United Arab Emirates and have plans to expand into this market.

While many companies around the world have years of experience in general water treatment, Spanish companies have some of the strongest backgrounds globally in the field of desalination plants. "We want to focus more on desalination," says Jose Maria Ortega, international commercial director of Pridesa, which builds and manages a variety of water treatment and purification plants in addition to desalination. "We think that it's probably the most significant strength of the company and the field where we feel we can differentiate ourselves compared to the rest of the companies all over the world."

According to the United Nations Environmental Programme, hundreds of scientists around the world see water shortage as one of the top concerns in the new millennium. Spanish companies are planning to use their expertise in desalination to improve the water situation for millions of people around the world, by dipping into the nearly limitless seas.

Resources

ICEX (Spanish Institute for Foreign Trade)
www.us.spainbusiness.com

AEDYR (Spanish Desalination and Water Reuse Association)
www.aedyr.com

AMEC URBIS (Spanish Association of Urban and Environmental Equipment)
urbis.amec.es

Centro de estudios hidrográficos
(The Center for Hydrographic Studies)
cedex.es/ingles/hidrograficos/presentation.html

HISPAGUA (Spanish Water Information System)
hispagua.cedex.es

SERCOBE (Spanish National Association of Manufacturers of Capital Goods):
www.sercobe.es

For more information visit:
www.us.spainbusiness.com

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ICEX
Spanish Institute for Foreign Trade

Forward

MEDICINE

Cancer's "World Wide Web"

Lung image database breathes life into "medical grid" vision

For several years, clinicians and computer scientists in the U.S. and abroad have been trying to improve cancer care—from diagnosis to treatment—by building vast, interconnected databases full of patient information. They call these repositories "medical grids" and envision the day when a physician in Strasbourg or New Delhi can see, for example, that an indecipherable image of a patient's lung is very similar to that of a San Francisco patient, whose case history could inform the decision to perform a biopsy or not. These nascent databases include not only patients' medical histories, including such data as MRIs and CT scans, but also information about how they have responded to drugs.

The benefits of these under-construction grids have been slow to come, partly because of technical problems and partly because federal privacy rules make data sharing difficult. But a National Cancer Institute project could test a multihospital system for comparing lung cancer images as early as this year—a clear move toward putting grids to use.

Kenneth H. Buetow, director of the institute's Center for Bioinformatics in Bethesda, MD, calls it a crucial first step toward "a World Wide Web of cancer research."

For the past year, Buetow and his team have collected more than 50,000 images of lung cancers obtained from medical trials and archived them in a secure electronic repository at NCI. Their effort is part of a three-year, $60 million pilot project launched in 2004, which involves 50 cancer centers and more than 600 researchers.

With the database now largely in place, testing is imminent. Buetow's team has set up a website accessible to cancer specialists. The next goal is to enable software that will automatically compare new images of lungs with those already aggregated in the database. Algorithms will search for commonalities and build a directory of the likeliest matches. Clinicians in offices and hospitals will be able to contrast the resulting lung images with the scans they need to evaluate.

Comparing images is just the first step. If all goes well, within three years Buetow hopes to conduct one or more clinical trials where a vast amount of medical data about lung cancer—including images, types of tumors, drug courses, patient outcomes, even

continued on page 22

ALEX NABAUM

METRICS

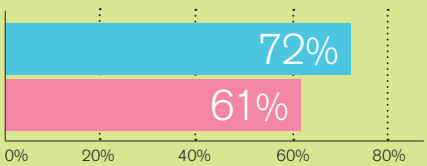
Malware Menace

Malware has gone from being an annoyance to being a destructive and costly threat to the Internet's viability. "Malware" is the general term (encompassing "spyware" and "adware") for code that lodges on your computer when you download software, visit certain websites, or open infected files attached to spam e-mails. Once in your PC, it sends out more spam, dispatches pop-up advertisements, steals your personal information, or tracks and reports on your Web behavior.

Infection statistics are hard to pin down, because malware purveyors constantly shift strategies to avoid detection, and there is no central regulator or common gatekeeper tracking code across the Internet. But a number of private and consumer groups generated metrics in late 2005.

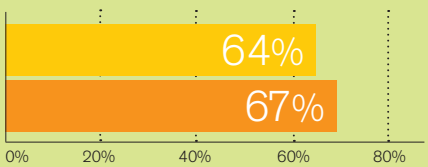
DAVID TALBOT

Percentage of PCs infected



Sources:
WebRoot
AOL/National Cyber Security Alliance

Percentage of e-mail that is spam



Radicati
Commtouch Detection Center

Average number of infections on U.S. consumer PCs
24
WebRoot

Annual average repair cost per consumer
$265
Radicati

Total annual cost to consumers
$3.5 billion
Consumers Union

Number of websites that host spyware
>360,000
WebRoot

the molecular profiles of the disease—would be used by physicians studying specific cases. The outcomes of these cases would be compared to those of cases treated through conventional approaches to cancer diagnosis. That comparison should yield information not just about the medical response of the patients but also about the accuracy with which the doctors made their diagnoses.

Medical-grid researchers are not short on vision. Comparing images is just the first step. In cases where the scans match, doctors hope to be able to bore deeper into the histories of similar cases and learn which drugs or surgeries worked best. And Buetow says his trials could actually hasten the day when some cancer diagnoses are automated. A doctor could input images (and as the grid expands, blood test results, descriptions of genetic markers, and other patient data) and learn how frequently near-identical test results from patients around the world correlate with specific malignancies such as lymphomas, melanomas, or sarcomas. And in the future, as gene-sequencing costs come down, the NCI's grid could even include patients' genomic information. "The power of the grid is in its capability to aggregate and correlate more and more public-health data from around the world," said Mary Kratz of the University of Michigan Medical School, a technical advisor to the grid research community. "The more data you have, the more knowledge you generate."

Meanwhile, mundane technical problems need solving. Since the data that accompany images vary in type and format from hospital to hospital, researchers are developing standard formats that can harmonize them all. "We're asking researchers at many competitive institutions to tear down barriers to sharing vast amounts of data," says Howard Bilofsky, senior fellow at the Center for Bioinformatics at the University of Pennsylvania, which participates in NCI's project. "Being able to share information in grids across the world in the arena of life science research is not something that is easily done."

TOM MASHBERG

INTERNET

Very Spammy!

Startup's software warns of spyware, spam

You've done your Internet search. Tantalizing links clamor for your attention. But it's hard to know which might contain spyware or throw you into the clutches of a spammer *(see "Malware Menace," this page)*. A Boston-based startup, SiteAdvisor, is beta-testing a tool to sort the good from the bad. With SiteAdvisor's software, one of three icons will appear next to many links—a red *X* signifying "stay away," a yellow exclamation point suggesting reason to worry, or a green check mark for the all-clear. If you visit a site, warning balloons may pop up saying things like "After entering our e-mail address on this site, we received 197 e-mails per week. They were very spammy."

The software was developed by two MIT-trained computer scientists, Doug Wyatt and Tom Pinckney, and consists of Web crawlers that roam the Internet, downloading proffered software and filling out sign-on forms to see what happens. The resulting knowledge is combined with information from the open-source security community and website owners and users. "In some sense, you can think of this as a search engine—except instead of trying to find content and relevance, we are trying to find out safety information you can use," Wyatt says. SiteAdvisor launches in March as a free download. Upgraded, fee-based versions are expected later this year. DAVID TALBOT

Q&A

Getting Personal about Drugs

Genetic tests are poised to revolutionize prescription writing

The age of "personalized medicine" has arrived, but chances are your doctor doesn't know it yet. Existing tests can analyze patients' genetic makeup to provide guidance on whether certain drugs—such as codeine, antidepressants, and even some cancer medications—will help them, harm them, or do nothing. And a host of even newer "pharmacogenetic" tests are now in the R&D pipeline.

But the existing tests aren't widely ordered by doctors, a fact that bothers David Flockhart, chief of clinical pharmacology at the Indiana University School of Medicine. Flockhart, who has developed genetic tests to help guide the prescription of diabetes and high-blood-pressure drugs, says doctors are generally uneducated about the availability of such tests. But he predicts that that will change if the U.S. Food and Drug Administration recommends that doctors test two specific genes in all patients prescribed a widely used anticoagulant.

TR: In November, an FDA advisory subcommittee you sit on recommended genetic testing for patients being prescribed warfarin, a drug used to treat blood clotting and stroke. Why did you make this recommendation?

David Flockhart: If the FDA accepts the recommendation, this will mean that it suggests everyone prescribed this valuable medication receive a genetic test at the start of warfarin treatment in order to ensure less costly and medically simpler treatment courses in which patients have fewer bad bleeding episodes and reach a stable, effective dose more quickly. It will bring pharmacogenetics for the first time to thousands of general practitioners and family practitioners.

But the FDA has already approved a number of genetic tests to guide prescriptions. Aren't doctors using them?

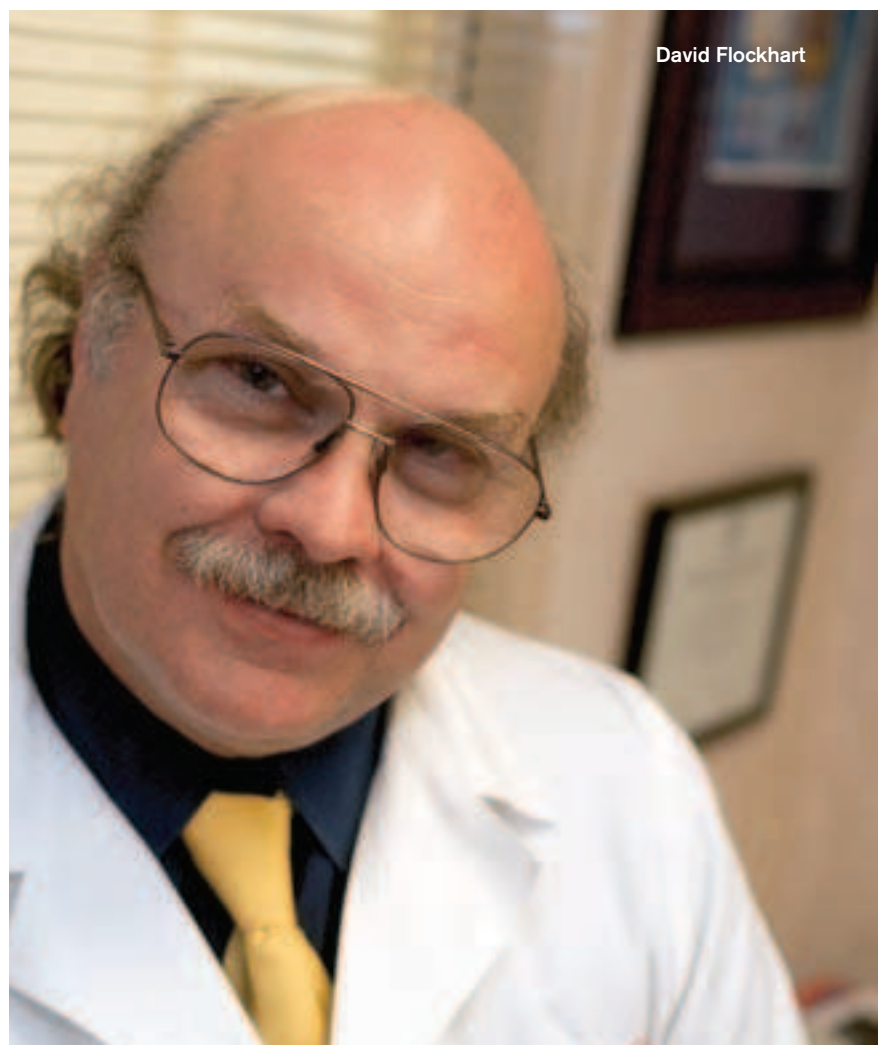
No. The big, big market is going to be in doctors' offices and hospitals, but it's really only now starting there. A major problem is going to be educating physicians who are, as yet, relatively uneducated about the availability of genetic tests to guide some of their prescribing decisions.

How long will that take?

Every one of the large clinical-testing labs is jockeying for position to try to exploit the large, anticipated growth in this kind of testing. The movement of these tests into the clinic will happen gradually with fits and starts....Demand will kick in within a year or two, as patients realize the power of these tests. That will be the biggest driver.

Are some diseases or drugs receiving more emphasis?

All branches of medicine and all the big, important diseases are under study. The size of the current effort to exploit the human genome sequence and bring that to the clinic is truly massive. The National Institutes of Health have made cardiovascular disease a priority, but it is clear that the psychiatric utility and tests used in oncology will also be important. The FDA recently approved a test to guide the use of irinotecan to treat colon cancer. A new test that will predict the effectiveness of tamoxifen for breast cancer patients is coming. Patients may first encounter these tests in the offices of psychiatrists and in hospital oncology practices. **ERIKA JONIETZ**



David Flockhart

TYAGAN MILLER

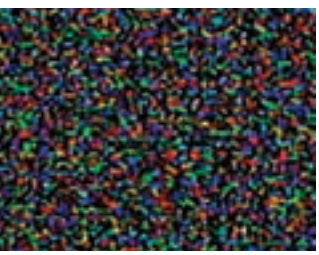
SOFTWARE

A Photo's Fingerprint

Software matches images to specific digital cameras

When a gun is used in a crime, forensic investigators identify it by the unique pattern of scratches that its barrel leaves on bullets. A similar trick is now being used to match digital images to the cameras that captured them, an important advance as child pornography crimes increase. Software developed by Jessica Fridrich at the State University of New York in Binghamton exploits the fact that every digital camera introduces a unique pattern of imperfections, or "noise," into its images. In monochrome areas, for example, individual pixels might actually be slightly different colors. Fridrich's software determines a camera's noise signature by identifying the irregularities in its pictures. That yields a "fingerprint" that investigators can search for in other photos. Fridrich tested her software using 10 cameras and a total of 3,000 pictures. In every case, the software matched the picture with the right camera, she says. "This is very nice work in the exciting and important problem of camera ballistics," says Hany Farid, computer science professor at Dartmouth College. Fridrich is currently seeking a patent and says the FBI is evaluating the technology as an investigative tool. The need is great: between 1996 and 2002, the number of federal cases involving child pornography exploded from 113 to 2,370, and the FBI predicts the trend will continue.

KATE GREENE



In this camera "fingerprint," color intensity corresponds to pixel noise levels.

NEUROSCIENCE

Brain Trainer

How to conquer cognitive decline, one game at a time

At a retirement community in San Francisco, a 71-year-old woman is having her brain trained. She sits at a computer, poised to react to a sequence of sounds, like "baa, tack, tab, cat." As she hears them, she clicks on the written equivalents on the computer screen. As her speed and accuracy improve, the sounds come faster, the sequences grow longer. The process, researchers say, could give her more years of auditory acuity.

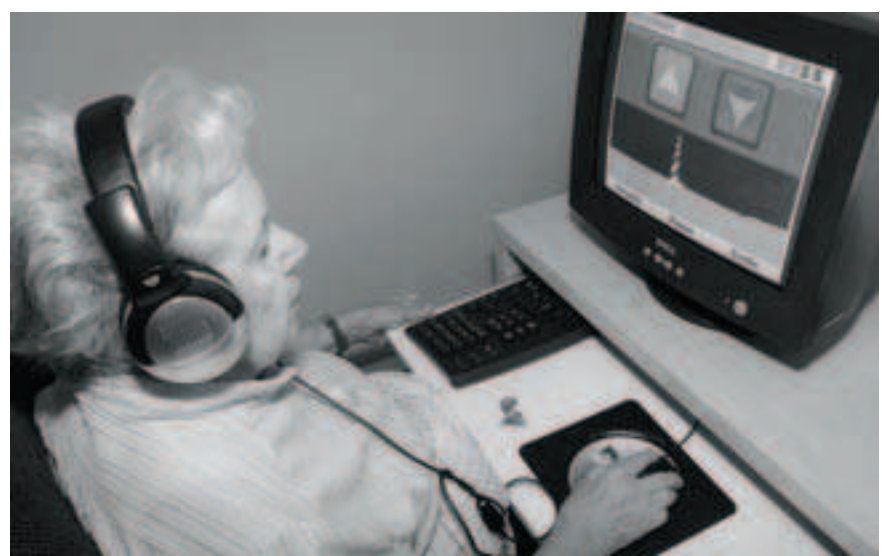
Procedures like this one are a step toward realizing a radical vision: stopping, or at least forestalling, cognitive decline using interactive technologies. It's the vision that animates the work of Michael Merzenich, a neuroscientist and cofounder of Posit Science in San Francisco, which is developing what he calls a "brain fitness program"—a set of interactive training exercises for the mind. "If you haven't played violin seriously for 10 years, you could recover your mastery with intensive practice," says Merzenich, a professor at the University of California, San Francisco. "That's what we're trying to achieve with training."

The auditory-skill software program for elderly patients is Posit's first project and has just reached the market. Researchers at Posit are now developing similar technologies to sharpen visual perception and fine motor control and envision additional ones to aid problem solving and balance. While other cognitive training programs focus on things like memory exercises, Posit's program exploits the concept of "plasticity"—our brain cells' ability to form new connections as we observe the world around us. "Merzenich has been a leader in the neuroscience of neural plasticity," says Charles Decarli, a neurologist at the University of California, Davis, who is running clinical trials of the program. "Now he's translating that basic science into this technology."

Last fall, Merzenich's team announced promising results from a preliminary clinical trial of 95 people with an average age of 80. After 40 hours of training over eight weeks, half the participants gained ten years in memory, meaning 80-year-olds had memories as sharp as 70-year-olds'. Posit is now testing the auditory program on middle-aged people and Alzheimer's patents to see if it will have the same benefits it did for healthy octogenarians. It expects preliminary results this spring.

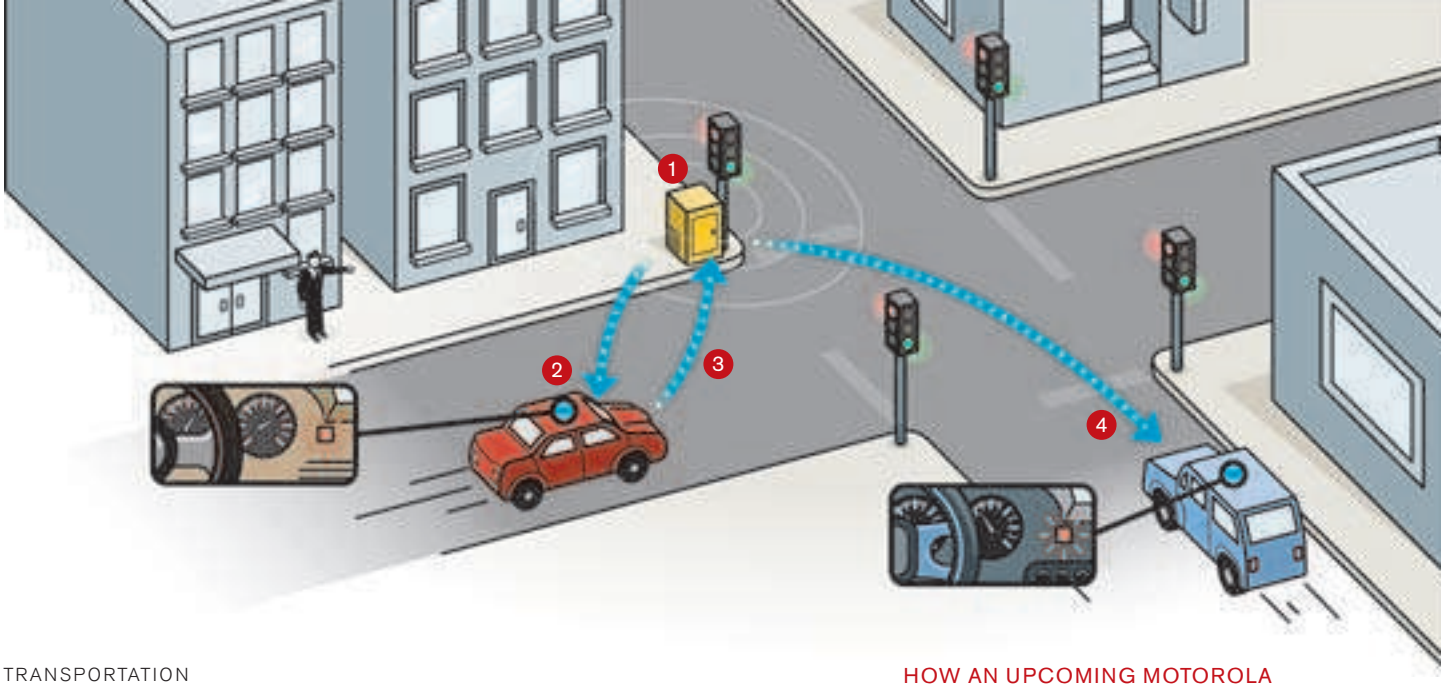
Posit is one of several companies developing cognitive training programs. But Jeffrey W. Elias, a health science administrator at the National Institute on Aging in Bethesda, MD, cautions that scientists still need to show that cognitive training in a particular task—such as listening to and remembering a sequence of sounds—can improve a person's ability to engage in daily activities in the real world. Still, "the potential is significant," he says.

EMILY SINGER



Below: An elderly woman hears sounds and clicks a mouse in response. Interactive workouts may improve her cognition.

COURTESY OF JESSICA FRIDRICH (FINGERPRINT); COURTESY OF POSIT SCIENCE (BRAIN TRAINER)



HOW AN UPCOMING MOTOROLA TEST IN MICHIGAN WILL WORK

1: Transponder beams out GPS location and color of traffic light to nearby cars.
2: Red car uses its GPS data and speed to calculate that it might run light, warns driver.
3: Red car sends warning that it might run light; roadside unit relays the warning.
4: Blue car receives relayed signal, warns driver that another car might run the light.

TRANSPORTATION

Wireless Highway

Networked-car safety research hits the road

A few months ago in Michigan, a sedan, followed by a minivan—both rigged out with prototype wireless communications equipment and software—swung onto Halsted Road in Farmington Hills. The driver of the sedan then slammed on his brakes, as if a dog had run in front of his bumper. This is the kind of abrupt move that can cause a rear-end crash, especially when visibility is poor.

But this particular sedan had a computer in its trunk outfitted with a Global Positioning System receiver and a short-range radio. The abrupt brake-jamming registered on the computer, which broadcast a warning and the sedan's GPS location. The minivan, similarly equipped, picked up the warning via special radio frequency, calculated that the sedan's location was just ahead of its own, and warned the driver, sounding a chime and flashing a red light.

The vehicles were testing Motorola communications technology as part of a corporate and government push to blanket roads with wirelessly broadcast safety information over the next decade, saving lives by getting cars' computers to talk to each other. To be sure, communications-driven auto safety features have been envisioned for years. But Motorola's tests are part of a new wave of projects that are using such technology in actual vehicles, on public roads, for the first time. "There are possibilities for information exchange that hitherto were only imagined," says James Misener, program leader in transportation safety research at the University of California, Berkeley.

One reason for that explosion of possibilities is that late-model cars are already loaded with sensors. Computers in today's cars track dozens of driving parameters, like when antilock braking systems are activated, the rate of deceleration, and when temperatures near the road surface near freezing. This kind of data could help other cars avoid hazards—and each other—if shared in the right ways.

For example, in Southfield, MI, the state Department of Transportation has outfitted light poles at intersections with transponders made by Azulstar, the wireless-networking firm. These gadgets can broadcast a traffic light's GPS position and its state: red, yellow, or green. Approaching cars equipped with prototype computers can examine this data, together with information on speed and location, and alert drivers who seem likely to run red lights.

And as part of the Motorola project, transponders housed in small gray boxes have been affixed to light poles along several kilometers of local streets in Farmington Hills. The roadside radio units have a range of 1.6 kilometers. Vehicles could collaborate with transponders to relay data across long distances to give drivers farther afield advance notice about conditions ranging from bad weather to dangerous road conditions to accidents.

While 10 states plan to participate in similar tests, Michigan says its roads will soon have the largest number of specially equipped vehicles and roadside transponders. Later this year, Chrysler will outfit a batch of cars with autonomous communication systems and test them itself in Auburn Hills and Southfield.

This rash of testing represents a changing approach to auto safety. Despite years of incremental efforts to make vehicles safer—air bags, antilock

continued on page 26

INFOGRAPHIC BY FUNNELINC.COM

GAMES

Xbox U

The college students glued to video game consoles today are as likely to be scholars as slackers. More than 100 colleges and universities in North America—up from less than a dozen five years ago—now offer some form of "video game studies," ranging from hard-core computer science to prepare students for game-making careers to critiques of games as cultural artifacts.

Recognition by the academy marks a coming of age for gaming. "When the School of Cinema-Television was founded 75 years ago, many people still considered film nothing but simplistic entertainment—a medium that could never be considered important artistically," says the University of Southern California's Scott Fisher, referring to USC's famed film school. "Games are considered by many people today in the same way. But the next generation of game designers has the potential to change that." The interactive-media division at USC, which Fisher chairs, offers bachelor's and master's degrees in interactive media, with courses like game history and theoretical tools for creating games.

Randy Pausch, codirector of the Entertainment Technology Center at Carnegie Mellon University—which offers a master's degree in entertainment technology—adds that gaming studies have a sneaky side: they attract students to computer science. Meanwhile, on the lit-crit front, some scholars have come up with a fancy name for their discipline: ludology, from the Latin *ludus* (game). Topics range from game philology to the study of virtual economies in EverQuest.

Academic video-game departments are also cranking out workers for hundreds of video game studios. "The school system can turn out our worker bees," says Jason Della Rocca, executive director of the International Game Developers Association.

DAVID KUSHNER

brakes, pretensioning seatbelts—the number of annual U.S. traffic fatalities has remained above 40,000 for a decade, partly because the total numbers of vehicles on roadways continues to increase. "We've kind of reached the end of the road with passive safety," says Steve Speth, director of the Vehicle Safety Office at the Chrysler Group.

Now the emphasis is on using wireless technology to help drivers actively avoid accidents—especially at intersections, the site of 17 percent of vehicle fatalities. "Once we start connecting vehicles, we will see a reduction in the total number of fatalities," says Peter Sweatman, director of the University of Michigan Transportation Research Institute in Ann Arbor. "That really is the future direction of auto safety."

The Federal Communications Commission has set aside a swath of radio bandwidth strictly for short-range communications on the nation's roads. It's an essential provision: cellular telephone networks do not establish connections fast enough.

Wireless auto safety still faces roadblocks, like questions about carmakers' liability if, say, the technology doesn't prevent a crash. But Ford, General Motors, DaimlerChrysler, and Nissan have linked up with the Michigan DOT to perform experiments like Motorola's. And they're joining with Toyota, BMW, and Volkswagen for collision avoidance tests on public roads. Some applications could be in cars soon; Ford, for example, plans to start tests in 2007 for possible production by 2011. **PETER DIZIKES**

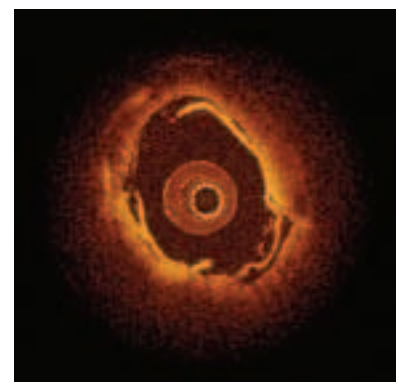
PHOTONICS

Optical Biopsy

Current heart-imaging techniques can identify arterial plaques, but they can't distinguish stable plaques from unstable ones likely to break off and cause clots. A relatively new laser imaging technology called optical-coherence tomography, on the other hand, can.

An early version of the technology, developed by James Fujimoto's research group at MIT, is already used in several countries to diagnose eye disease. A laser beam is split in two; one beam is reflected off eye tissue. The reflection and the other beam are combined to create interference patterns that can be converted into an eye image. But in an artery, the technology can image only about three centimeters in 30 seconds, the maximum time that blood flow can be safely blocked.

MIT postdoc Robert Huber and Fujimoto describe using a laser whose light frequency can be tuned extremely rapidly to enhance imaging speed. To allow faster tuning, the researchers built a laser with a coil of optical fiber several kilometers long. The round-trip time of the light in the coil precisely matches the time between frequency adjustments, so the beams provide a ready supply of photons for each adjustment, eliminating the delays normally required to build up enough photons at a new frequency. The technology can scan three centimeters of artery in just 2.5 seconds, at a high enough resolution to diagnose plaques and distinguish cancerous cells from normal ones. LightLabs Imaging, an MIT spinoff, is working on a prototype and hopes to be ready for clinical trials before 2008. **NEIL SAVAGE**



New laser imaging technology shows damage to the lining of an artery. The circles are optical fiber in its sheath.

FRED RIX (XBOX U); COURTESY OF LIGHTLAB IMAGING (BIOPSY)

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BIOTECH

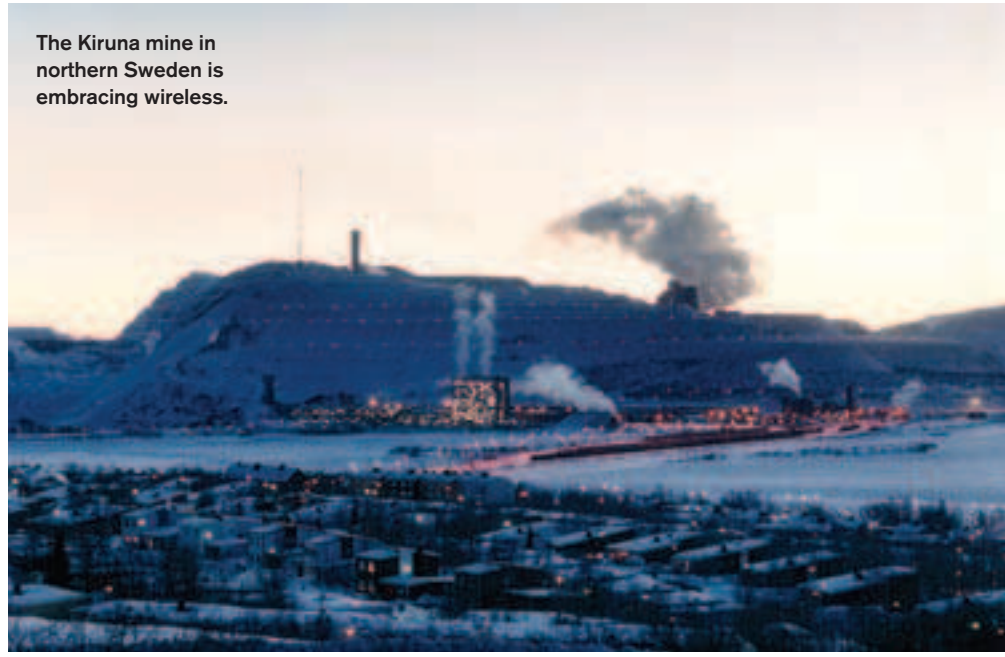
Antibody Alternative

In the last decade, antibody-based drugs have provided treatments for allergies, infectious diseases, cancers, and autoimmune diseases such as rheumatoid arthritis. But antibodies are large molecules, expensive to manufacture and tricky to maintain, requiring refrigerated storage. And extensive patent protections tie the hands of drug companies that want to expand their use.

Now researchers at biotech startup Avidia, in Mountain View, CA, have engineered a new class of proteins they call "avimers," which the company says are easier to make and store—and require fewer lawyers to bring to market. Avidia scientists have shown that an avimer designed to inhibit human interleukin-6 (IL-6)—a protein implicated in rheumatoid arthritis and Crohn's disease—works in mice. Avidia plans to move the avimer into human trials later this year.

Avimers derive from a related group of about 200 human-protein subunits. In the body, collections of these subunits fit together like Legos to form proteins that bind to small molecules and other proteins—exactly what any drug must do. Avidia scientists have varied the molecules' building blocks to create a vast "library" of more than 100 million billion subunits. Linking together differing numbers and types of the variants "allows you to engineer proteins with a desired specificity for a target and to get very high affinities," says George Georgiou, a protein engineer at the University of Texas at Austin.

Avidia scientists say they can design molecules to either inhibit or activate their targets and perhaps even bind to multiple targets simultaneously. Josh Silverman, an Avidia senior scientist, says the company's initial sights are on drugs for cancers and autoimmune diseases. ERIKA JONIETZ



The Kiruna mine in northern Sweden is embracing wireless.

COURTESY OF LKAB

WIRELESS

Underground Wi-Fi

Cities may wait, but mines get full wireless broadband coverage

For most of us, it's remarkable enough to access the Internet from a plane 10,000 meters in the air. But when Swedish process-control engineer Ulf Olsson does that—as he did recently while flying over Arizona—he's also monitoring an iron-ore drill 1,000 meters below the earth's surface in northern Sweden, thanks to underground Wi-Fi.

While cities like Philadelphia wait for citywide Wi-Fi networks to come on line, the world's iron, coal, and copper mines are getting fat wireless broadband pipes. By early next year, the mine in Kiruna, Sweden—150 kilometers north of the Arctic Circle—will complete its installation of Wi-Fi-linked drills. A German mining company, Deutsche Steinkohle, is installing several hundred Wi-Fi hot spots in its coal mines. So is a copper mine in Chile called El Teniente, which claims to be the world's largest.

Miners aren't blogging from the tunnels—yet. In Kiruna, information from drills and trucks—such as their positions and the weight of their loads—is relayed via wireless base stations to a computer in a control room above ground. (Weight is an important datum; it tells the operator how good the ore is. The heavier the better.) With Wi-Fi networks, fewer miners have to face the risks of working underground—and those who do have a more durable link to the outside.

LKAB, the company that operates the Kiruna mine, has experimented with wireless networks before, but Wi-Fi offers cheap standardized components and is the newest tool for boosting mine safety and productivity, says Christoph Mueller, president of Embigence, an automation company in Ladbergen, Germany. "Mine companies can't build bigger machines. Now productivity growth has to come from optimization," he says. With Wi-Fi, he says, mining companies gain cheap real-time information—and workers stay safe. PATRIC HADENIUS

ROCHESTER, NEW YORK.

Rochester Philharmonic Orchestra at the Eastman Theatre

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Players in this "orchestra" follow IMs, not batons.

COMPUTER MUSIC

Boston Pop-Ups

Newest thing in wireless networking: the "laptop orchestra"

Computer musicians fiddle with sampled sounds and write software, but theirs is often a lonely pursuit. Now a few at the vanguard are tapping the musical potential of networked laptop computers. In April, an ensemble called the Princeton Laptop Orchestra will hold its first concert—and solemnly perform a piece inspired by the social call-and-response patterns of swamp frogs.

Fifteen student musicians will sit atop pillows before their laptop-instruments, awaiting their conductor's signals, which will arrive via instant messages or pop-ups. Then they'll tap into all sorts of presampled, live, and computer-generated sounds (such as sampled drumbeats, or their own voices reciting the alphabet) and manipulate them with gizmos like glove-mounted accelerometers. Like the frogs, who reply to one another with different sorts of croakings, the musicians will reply to one another with different noises. Tod Machover, the avant-garde musical inventor and composer at MIT's Media Lab, calls the orchestra "a cooler, better way to teach a new music environment than any I've heard of."

The orchestra's cocreator, Perry Cook, a Princeton professor of computer science and music, acknowledges that the computers haven't made performing easier or cheaper; it takes 40 minutes just to set up the wireless network that synchronizes the expensive laptops. So traditional musicians need not see the technology as a threat; if you wanted to play a Beethoven symphony, "it'd be much cheaper to use a traditional orchestra" than the laptop version, Cook says. For now, the ensemble's aspirations are modest: to survive the semester and become a Princeton fixture. **JESSICA BAKER**

MATERIALS

Finally, Better Batteries

Graphite "foam," nanotech-enabled lithium surge to market

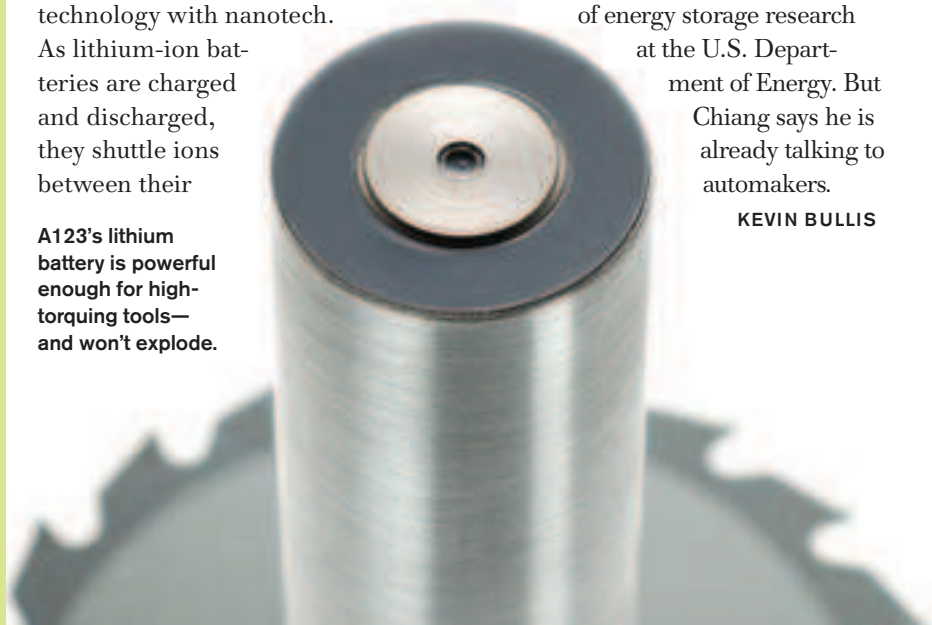
After years in which consumers and researchers faced sharp trade-offs in weight, safety, and power for high-power batteries, promising variants are emerging. Nanotechnology is enabling a new lithium-ion battery that can unleash five times as much power as existing versions, and this summer, tool manufacturer DeWalt, of Baltimore, MD, plans to sell a line of 36-volt cordless tools that use it. Progress in the field even includes an upgrade to the age-old lead-acid battery.

The new lithium battery—developed by A123 Systems of Watertown, MA, and based on the work of Yet-Ming Chiang, a materials scientist at MIT—is not only more powerful but also recharges to 90 percent capacity in five minutes and lasts through ten times as many recharging cycles as conventional counterparts, the company says. The battery will initially be used in professional-grade tools where bursts of high power are at a premium. But the technology could lead to battery-operated versions of power-hungry devices like vacuum cleaners, lawn mowers—even hybrid cars.

Chiang improved lithium-ion technology with nanotech. As lithium-ion batteries are charged and discharged, they shuttle ions between their electrodes. Shrinking the size of the lithium particles can increase the batteries' power, but it can also incline them to explode. Chiang started with safer but poorly conductive materials and borrowed a trick from the semiconductor industry—"doping" one material with trace amounts of another—to make them conductive. Then he shrank the doped particles, making it easier for ions to escape. Nail-puncture tests that cause conventional lithium-ion batteries to burn produces only a wisp of vapor, the company says.

A123 Systems is not the only company changing the battery game. Firefly Energy of Peoria, IL, is redesigning lead-acid batteries and developing them for use in military vehicles and lawn tractors. Firefly replaced some of the battery lead with a graphite foam that has a much greater surface area. This cuts weight, extends longevity, and puts the batteries in the same performance category as the nickel–metal hydrides in hybrid cars, says cofounder Mil Ovan.

As yet, no proposed batteries offer the 15-year lifetime needed for hybrids, says David Howell, manager of energy storage research at the U.S. Department of Energy. But Chiang says he is already talking to automakers. **KEVIN BULLIS**



A123's lithium battery is powerful enough for high-torquing tools—and won't explode.

COURTESY OF PRINCETON UNIVERSITY (POP-UPS); CHRISTOPHER HARTING (BATTERIES)

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Jonathan Zittrain

Preëmpting an Internet clampdown

Is it possible that a spectacularly productive era of Internet-driven innovation will soon end, amid new government and corporate controls cheered by millions of turned-off consumers? Yes, says Jonathan Zittrain, professor of Internet governance at the University of Oxford, cofounder of Harvard Law School's Berkman Center for Internet and Society, and author of "The Generative Internet," an upcoming article in the *Harvard Law Review*. Machines clogged with "malware"—the catchall term for code that infiltrates PCs to steal data, send out spam, or produce pop-up messages—are already costing billions annually and testing everyone's tolerance, Zittrain says. And a single destructive virus could prompt harsh regulations and cause millions of people to seek safe, closed networks.

To help fight back, Zittrain and fellow academics have just launched a new antimalware effort (www.stopbadware.org) funded by Google, Sun Microsystems, and Lenovo (the Chinese firm that acquired IBM's PC division). Zittrain describes how this effort fits into the Internet's history and proposes a possible next step in preëmpting the stifling of the Net.

TR: What do you feel is at stake here?

Zittrain: The history of the PC and the unfettered Internet has shown us just how important amateurs working in obscure corners can be as a source of wildly popular and transformative applications. The capacity for uncoördinated third-party contribution makes the PC and Internet highly generative, and we can thank it for the World Wide Web, instant messaging, blogging, Wikipedia, and even online shopping. It's a world away from the walled-garden proprietary online services like CompuServe and Prodigy of the 1980s, and from that era's non-PC "information appliances" like LCD-screen digital typewriters and video-game consoles.

Of course, there's a downside or two.

These generative characteristics carry with them the seeds of their own destruction. Generativity can mean excess and outright disruption. Publishers have seen this when a couple teenagers can brilliantly engineer a peer-to-peer network that enables copyright infringement. So far, regulators have had a comparatively light touch going after such activities. I think a watershed in the security space—for example, a mass-distributed virus whose payload wipes out hard drives—could change consumer sentiment so that a controlled information environment is appealing to many more people. These controlled platforms, while great for what they do, foreclose exactly the sort of innovation that brought us all the great applications. And if we lose people, we won't be as easily able to include them in the critical mass for any project that relies on broad-based adoption. The status quo is not stable.

Many people let companies like Symantec guard the door 24-7, while Microsoft and Apple automatically update their operating systems. Won't this prevent your "watershed" crisis?

This risks turning PCs into gated communities that can too easily become prisons patrolled by a single warden. Suppose a security vendor or OS maker, through its success against badware, starts collecting user proxies to decide what will and won't run on nearly everyone's machine and enforces those decisions through near-instant automatic updates. This not only creates an antigenerative architecture with a gatekeeper like the days of Prodigy and AOL, but it also offers a way for regulators to demand that such gatekeepers eliminate code deemed socially—rather than technologically—bad or to insert new code for individual surveillance. To be sure, the actions by the biggest players so far have been measured. Microsoft currently distinguishes between critical security updates and others that are merely suggested.

So what will www.stopbadware.org do that's so different?

First, we need to deeply understand the problem of bad code—code that will turn people away from participation in the generative Internet—as something more than technical. This includes policy and legal issues that automatic antivirus detectors are, of course, not built to address. Second, we want to marshal a solution that does not cause new problems of centralized control. We can do this on both the input and output sides: developing and distilling evaluations of code in ways that consumers can understand—especially since there is a variety of risk tolerance among them—and in which they can participate.

Surely average PC owners can't evaluate new code to gauge risks or even regularly consult a new website. What do you hope to offer them?

Imagine, for example, a simple display, a networked "dashboard" where users contemplating code can contribute to—and then read—simple demographics like how many other people are running it, how many were running it last week, and whether the computers running it appear to be better off with it on board. If enough people participate, meaningful—and currently unobtainable—data can be collected and packaged to keep genuine choice in the hands of the user. That's a generative solution to a generative problem.

DAVID TALBOT

ASIA KEPKA

BIOTECHNOLOGY

Assessing the Threat

To predict bioweapons' effects, we need more data.

By Allison M. Macfarlane

Could terrorists, intent on causing as much harm and societal disruption as possible, use new biotechnology processes to engineer a virulent pathogen that, when unleashed, would result in massive numbers of dead? Mark Williams, in his article "The Knowledge" *(see p. 44)*, suggests we should be contemplating this doomsday scenario in the 21st century. Williams's article might make you sleep less soundly, but are the threats real? The truth is that we do not really know.

Part of the problem is that even if terrorists could create new pathogens virulent to humans, it's not at all clear that they could "weaponize" them—that is, put the pathogens into a form that is highly infectious to humans and then disperse them in ways that expose large numbers of people.

Past experience suggests that this is not an easy task. During World War II, the Japanese dropped plague-infected materials on Chinese cities, to limited effect. In 1979, the Soviets caused 66 deaths from anthrax by accidentally releasing it from a bioweapons facility in Sverdlovsk. In 1984, the Rajneeshees cult contaminated salad bars in the Dalles, OR, with salmonella, but their actions killed no one. In 1993, the Aum Shinrikyo cult failed to kill anyone after carrying out multiple attacks with anthrax in Japan. Finally, the 2001 anthrax letter attacks in the U.S. killed five people. These were all frightening events. They were not, however, grave threats to national security.

Yet estimates of bioweapons dangers tend to be dire, like those in Williams's article. The truth is that the data are too thin to make accurate projections of the effects of bioweapons attacks. I surveyed seven separate estimates of fatalities from a projected anthrax attack. The lowest estimate, by Milton Leitenberg, ranged from zero to 1,440 dead per kilogram of anthrax used, while the highest, by Lawrence Wein and others, put fatalities between 123,400 and 660,000 per kilogram of anthrax. Most of these estimates were made on the basis of little actual data.

To predict accurately the effects of bioweapons, data are needed on the amount of agent required to infect a person, the percentage of people who survive an infection (which depends on the health of the population), the transmission rate if the agent is contagious, the ability to aerosolize and disperse an agent effectively (which depends, in turn, on climatic conditions), the environmental stability of an agent, the population density, and the abilities of the public-health system, including when an attack is detected and whether prophylactics, vaccines, or antidotes exist and, if so, in what quantities.

For any one pathogen—even one familiar to us, like smallpox and anthrax—not all of these variables are known, and therefore quantitative predictions are not possible with a high degree of certainty. In the words of the U.S. National Academy of Sciences in a 2002 report, "these factors produce an irreducible uncertainty of several orders of magnitude in the number of people who will be infected in an open-air release."

For example, data on the infectiousness of an agent varies widely, depending on the agent. Because of limited experience with anthrax, susceptibility data have often been extrapolated from animal trials that have little bearing on human response to agents. In the case of smallpox, with which scientists had much experience in the 20th century, some factors remain uncertain, such as the transmission rate.

In the models of bioweapons attacks, the ability to weaponize an agent and disperse it effectively is estimated in part from open-air trials done by the U.S. Army between the 1940s and 1960s. These trials used live simulants of agents on major U.S. cities, but the behavior of a real bioweapon agent in such a situation remains uncertain. Williams's article doesn't describe in any detail the ability of terrorists to weaponize any of the theorized agents. Yet making effective bioweapons would take a tremendous amount of work. While a state-sponsored program might have the means to do that work, terrorist groups probably don't. With so much uncertainty surrounding the outcome of a bioweapons attack, it does not make sense to plan extensive biodefense programs when more-certain threats, particularly those involving nuclear weapons, require attention. TR

Allison M. Macfarlane is a research associate in the Science, Technology, and Global Security Working Group in MIT's Program in Science, Technology, and Society.

BIOTECHNOLOGY

Light Bulbs Reinvented

Switch on OLEDs!

By Stephen Forrest

In 1985, Ching Tang and Steven Van Slyke of Kodak's R&D lab in Rochester, NY, demonstrated light-emitting devices based on thin films of fluorescent organic molecules. Although they might not have fully rec-

ILLUSTRATIONS BY OTTO STEININGER

ognized it at the time, their invention carried the possibility of transforming display screens and, perhaps more importantly, interior lighting.

But the invention had a significant drawback that was imposed by quantum mechanics. Making these organic molecules emit light requires injecting electrons from electrical contacts on the film surfaces. But because of quantum-mechanical considerations, only one in four electrons injected will produce light emission. As a result, fluorescent organic light-emitting devices (OLEDs) had relatively low efficiency.

In 1998, my group at Princeton University, in collaboration with researchers at the University of Southern California under the direction of Mark Thompson, found that including a heavy-metal atom such as platinum or iridium in the organic molecule could overcome the quantum-mechanical limitations, allowing for 100 percent of the injected electrons to result in light emission via the process of phosphorescence. Phosphorescence is often associated with dim, long-lasting light, but with the addition of a heavy metal atom, organic molecules are capable of both rapid and exceedingly bright phosphorescence.

This new phenomenon, called electrophosphorescence, allows OLEDs to be used in high-efficiency, full-color displays. But perhaps more importantly, it allows for the emergence of a new generation of interior illumination sources. By combining the light emissions of red, green, and blue electrophosphorescent OLEDs, we can generate light that the eye perceives to be white—and do it very efficiently.

Current incandescent interior lighting, which has been in development for over 125 years, has an efficiency of approximately 15 lumens per watt. Electrophosphorescent white OLEDs have already demonstrated efficiencies of approximately 20 lumens per watt at levels bright enough for room illumination. We recently demonstrated in our labs that by combining phosphorescence and more conventional fluorescence, we can make a single OLED structure that produces nearly 30 lumens per watt, with the possibility of 50 to 60 lumens per watt in the near future. This device operates at lower voltage than a pure electrophosphorescent white OLED, resulting in improved efficiency.

Higher-efficiency lighting can reduce humankind's ever increasing use of energy. OLEDs may play a vital role in the effort. TR

Stephen Forrest is vice president of research at the University of Michigan, Ann Arbor. He is also a professor in the Departments of Electrical Engineering and Computer Science, Physics, and Materials Science and Engineering.

INFORMATION TECHNOLOGY

Science as a Web Service

XML can supercharge research.

By Craig Mundie

Although my roots before joining Microsoft were in supercomputing, I believe that "extreme computing" and adding gigaflops (billions of floating-point operations per second) are no longer the optimal solutions to most scientific and technical problems. Today, scientists and engineers can buy or build 10-gigaflop desktop computers for around $5,000, and within the next several years, we will see similar supercomputing power at the chip level. Instead, the next breakthroughs in science and engineering will come from harnessing the power of software and data—for example, using low-cost sensors to collect terabytes of real-world data and using data management tools to understand it.

Of course, combining computer models and real-world data presents new challenges, particularly in learning how to store, search, analyze, visualize, publish, and record the provenance of that data and the resulting conclusions. I believe the software industry can play a key role in developing tools that automate these data management tasks.

Such tools are beginning to appear. Inexpensive databases that allow precious data to be stored in a structured format are readily available but are significantly underused by the scientific community. Another important software advancement is XML (the eXtensible Markup Language). XML allows sensors, services, and systems to easily exchange data. Data formatted with XML is easier to search, and because metadata is an integral part of XML, it allows the provenance of the data to be recorded.

XML is also one of the enabling technologies for grid computing and Web services, which will revolutionize the scientific community in the coming decade by enabling the free exchange of information across distributed systems. Remote computation will be directly accessible from any desktop, and sensors and instruments will have their own Internet addresses.

The immediate challenge for the scientific and engineering community is to take advantage of available data management and data analysis tools. The larger and longer-term challenge is for the leaders in academic research to leverage software and Web services technologies to standardize the way they present and track their data. TR

Craig Mundie is Microsoft's chief technology officer for advanced strategies and policy

Photo Essay

Biotech Drug Factory

Last year, Genentech, a global leader in the manufacture of genetically engineered drugs, had sales of about $5.5 billion. A "biotech drug" is one that uses a protein to treat a particular disorder: to make its protein-based drugs, which include cancer treatments and a human growth hormone, Genentech must grow vast quantities of therapeutic proteins in host cells and then harvest them. The company can ferment approximately 280,000 liters of cell culture at any one time at its various manufacturing plants. This photo essay illustrates the production process at Genentech's South San Francisco plant, from the testing and fine-tuning of manufacturing techniques, to the fermentation of cells, to the purification of drugs that will be shipped around the world.

By Kate Greene Photographs by Emily Nathan

To make its therapeutic proteins, Genentech first genetically modifies either Chinese hamster ovary (CHO) cells or *E. coli* bacteria, depending on the complexity of the desired protein. For mass production of the proteins, millions of the genetically engineered, protein-producing *E. coli* or CHO cells are added to a nutrient-rich growth medium *(this page)*.


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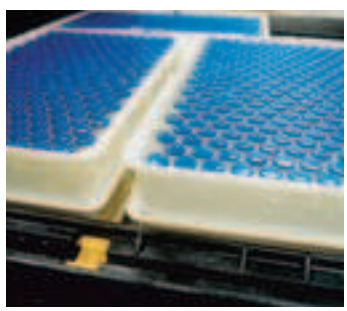
BIOTECHNOLOGY

Opposite page: Incubated in the medium, the cells multiply, creating many more millions of tiny protein factories. As the number of cells increases, so does the amount of medium needed—from as little as 200 milliliters to as much as 12,000 liters.
Left, top and bottom: While cells proliferate, chemicals are added and samples taken to measure pH levels, media composition, and the proportion of viable cells, which ranges from 90 to 100 percent.
Below: Genentech's manufacturing process is largely automated, but it still requires constant human monitoring. The pilot plant, pictured here, is where new production technologies and processes are developed and tested; both it and the other production facilities operate seven days a week, 24 hours a day.

Photo Essay

Center, above: Complicated networks of pipes keep pressure and temperature at appropriate levels in these 1,000-liter tanks *(top left)*. When the incubated CHO or *E. coli* cells reach an adequate volume, they are moved to the tanks, where they remain for as long as two weeks. The two cell types have different properties that lead to different kinds of protein products, so they also require different processing technologies to shield them from contamination. Employees must wear sanitized suits to protect both the proteins and themselves. *Bottom left:* After spending time in the 1,000-liter tank, *E. coli* cells are pumped into a homogenizer, where the high pressure bursts their cell walls, releasing their contents. Proteins and cell lysate are then pumped into a centrifuge, shown here, which separates desired proteins from unwanted cell remnants.

Above: CHO cells continue to grow in these 12,000-liter tanks, which span three floors. The proteins they secrete into the cell broth are ultimately harvested using centrifugation or filtration.
Top left: To extract the desired protein, Genentech pumps the feedstream through the large chromatographic columns that separate the therapeutic proteins from contaminants by exploiting their size and their characteristic charge distribution.
Bottom left: The last stage of the process further purifies the desired protein and replaces the buffer used in the previous chromatography step with a "human-friendly" formulation.
Bottom right: The final protein product is poured into small glass vials as they travel on a conveyor belt, headed for shipment.



Biotechnology's advance presents dark possibilities. Terrorists can develop biological weapons. Worse, the life sciences could give malefactors the ability to manipulate fundamental life processes—and even affect human behavior.

The Knowledge

By Mark Williams

In 1973, Soviet bioweaponeer Serguei Popov was a student in Novosibirsk, Siberia.

COURTESY OF SERGUEI POPOV

Last year, a likable and accomplished scientist named Serguei Popov, who for nearly two decades developed genetically engineered biological weapons for the Soviet Union, crossed the Potomac River to speak at a conference on bioterrorism in Washington, DC.

Popov, now a professor at the National Center for Biodefense and Infectious Diseases at George Mason University, is tallish, with peaked eyebrows and Slavic cheekbones, and, at 55, has hair somewhere between sandy and faded ginger. He has an open, lucid gaze, and he is courteously soft-spoken. His career has been unusual by any standards. As a student in his native city of Novosibirsk, Siberia's capital, preparing his thesis on DNA synthesis, he read the latest English-language publications on the new molecular biology. After submitting his doctorate in 1976, he joined Biopreparat, the Soviet pharmaceutical agency that secretly developed biological weapons. There, he rose to become a department head in a comprehensive program to genetically engineer biological weapons. When the program was founded in the 1970s, its goal was to enhance classical agents of biological warfare for heightened pathogenicity and resistance to antibiotics; by the 1980s, it was creating new species of designer pathogens that would induce entirely novel symptoms in their victims.

In 1979, Popov spent six months in Cambridge, England, studying the technologies of automated DNA sequencing and synthesis that were emerging in the West. That English visit, Popov recently told me, needed some arranging: "I possessed state secrets, so I could not travel abroad without a special decision of the Central Committee of the Communist Party. A special legend, essentially, that I was an ordinary scientist, was developed for me." The cover "legend" Popov's superiors provided proved useful in 1992, after the U.S.S.R. fell. When the Russian state stopped paying salaries, among those affected were the 30,000 scientists of Biopreparat. Broke, with a family to feed, Popov contacted his British friends, who arranged funding from the Royal Society, so he could do research in the United Kingdom. The KGB (whose control was in any case limited by then) let him leave Russia. Popov never returned. In England, he studied HIV for six months. In 1993, he moved to the University of Texas Southwestern Medical Center, whence he sent money so that his wife and children could join him. He remained in Texas until 2000, attracting little interest.

"When I came to Texas, I decided to forget everything," Popov told me. "For seven years I did that. Now it's different. It's not because I like talking about it. But I see every day in publications that nobody knows what was done in the Soviet Union and how important that work was."

Yet if Popov's appearance last year at the Washington conference is any indication, it will be difficult to convince policymakers and scientists of the relevance of the Soviet bioweaponeers' achievements. It wasn't only that Popov's audience in the high-ceilinged chamber of a Senate office building found the Soviets' ingenious applications of biological science morally repugnant and technically abstruse. Rather, what Popov said lay

EDITOR'S NOTE: *Conscious of the controversial nature of this article,* Technology Review *asked Allison Macfarlane, a senior research associate in the Technology Group of MIT's Security Studies Program, to rebut its argument: see "Assessing the Threat," page 34. We were also careful to elide any recipes for developing a biological weapon. Such details as do appear have been published before, mainly in scientific journals.*

so far outside current arguments about biodefense that he sounded as if he had come from another planet.

The conference's other speakers focused on the boom in U.S. biodefense spending since the attacks of September 11, 2001, and the anthrax scare that same year. The bacteriologist Richard Ebright, a professor of chemistry and chemical biology at Rutgers University, fretted that the enormous increase in grants to study three of the category A bacterial agents (that is, anthrax, plague, and tularemia) drained money from basic research to fight existing epidemics. Ebright (who'd persuaded 758 other scientists to sign a letter of protest to Elias Zerhouni, the director of the National Institutes of Health) also charged that by promiscuously disseminating bioweaponeering knowledge and pathogen specimens to newly minted biodefense labs around the United States, "the NIH was funding a research and development arm of al-Qaeda." Another speaker, Milton Leitenberg, introduced as one of the grand old men of weapons control, was more splenetic. The current obsession with bioterrorism, the rumpled, grandfatherly Leitenberg insisted, was nonsense; the record showed that almost all bioweaponeering had been done by state governments and militaries.

Such arguments are not without merit. So why do Serguei Popov's accounts of what the Russians assayed in the esoteric realm of genetically engineered bioweapons, using pregenomic biotech, matter *now*?

They matter because the Russians' achievements tell us what is possible. At least some of what the Soviet bioweaponeers did with difficulty and expense can now be done easily and cheaply. And *all* of what they accomplished can be duplicated with time and money. We live in a world where gene-sequencing equipment bought secondhand on eBay and unregulated biological material delivered in a FedEx package provide the means to create biological weapons.

Build or Buy?

There is growing scientific consensus that biotechnology—especially, the technology to synthesize ever larger DNA sequences—has advanced to the point that terrorists and rogue states could engineer dangerous novel pathogens.

In February, a report by the Institute of Medicine and National Research Council of the National Academies entitled "Globalization, Biosecurity, and the Future of the Life Sciences" argued, "In the future, genetic engineering and other technologies may lead to the development of pathogenic organisms with unique, unpredictable characteristics." Pondering the possibility of these recombinant pathogens, the authors note, "It is not at all unreasonable to anticipate that [these] biological threats will be increasingly sought after…and used for warfare, terrorism, and criminal purposes, and by increasingly less sophisticated and resourced individuals, groups, or nations." The report concludes, "Sooner or later, it is reasonable to expect the appearance of 'bio-hackers.'"

Malefactors would have more trouble stealing or buying the classical agents of biological warfare than synthesizing new ones. In 2002, after all, a group of researchers built a functioning polio virus, using a genetic sequence off the Internet and mail-order oligonucleotides (machine-synthesized DNA molecules no longer than about 140 bases each) from commercial synthesis companies. At the time, the group leader, Eckard Wimmer of the State University of New York at Stony Brook, warned that the technology to synthesize the much larger genome of variola major—that is, the deadly smallpox virus—would come within 15 years. In fact, it arrived sooner: December 2004, with the announcement of a high-throughput DNA synthesizer that could reproduce smallpox's 186,000-odd bases in 13 runs.

The possibility of terrorists' gaining access to such high-end technology is worrisome. But few have publicly stated that engineering certain types of recombinant microörganisms using older equipment—nowadays cheaply available from eBay and online marketplaces for scientific equipment like LabX—is *already* feasible. The biomedical community's reaction to all this has been a general flinching. (The signatories to the National Academies report are an exception.) Caution, denial, and a lack of knowledge about bioweaponeering seem to be in equal parts responsible. Jens Kuhn, a virologist at Harvard Medical School, told me, "The Russians did a lot in their bioweapons program. But most of that isn't published, so we don't know *what* they know."

On a winter's afternoon last year, in the hope of discovering just what the Russians had done, I set out along Highway 15 in Virginia to visit Serguei Popov at the Manassas campus of George Mason University. Popov came to the National Center for Biodefense after buying a book called *Biohazard* in 2000. This was the autobiography of Ken Alibek, Biopreparat's former deputy chief, its leading scientist, and Popov's ultimate superior. One of its passages described how, in 1989, Alibek and other Soviet bosses had attended a presentation by an unnamed "young scientist" from Biopreparat's bacterial-research complex at Obolensk, south of Moscow. Following this presentation, Alibek wrote, "the room was absolutely silent. We all recognized the implications of what the scientist had achieved. A new class of weapons had been found. For the first time, we would be capable of producing weapons based on chemical substances produced naturally by the human body. They could damage the nervous system, alter moods, trigger psychological changes, and even kill."

When Popov read that, I asked him, had he recognized the "young scientist?" "Yes," he replied. "That was me."

After reading *Biohazard*, Popov contacted Alibek and told him that he, too, had reached America. Popov moved to Virginia to work for Alibek's company, Advanced Biosystems,

and was debriefed by U.S. intelligence. In 2004 he took up his current position at the National Center for Biodefense, where Alibek is a distinguished professor.

Regarding the progress of biotechnology, Popov told me, "It seems to most people like something that happens in a few places, a few biological labs. Yet now it is becoming widespread knowledge." Furthermore, he stressed, it is knowledge that is Janus-faced in its potential applications. "When I prepare my lectures on genetic engineering, whatever I open, I see the possibilities to make harm or to use the same things for good—to make a biological weapon or to create a treatment against disease."

The "new class of weapons" that Alibek describes Popov's creating in *Biohazard* is a case in point. Into a relatively innocuous bacterium responsible for a low-mortality pneumonia, *Legionella pneumophila*, Popov and his researchers spliced mammalian DNA that expressed fragments of myelin protein, the electrically insulating fatty layer that sheathes our neurons. In test animals, the pneumonia infection came and went, but the myelin fragments borne by the recombinant Legionella goaded the animals' immune systems to read their own natural myelin as pathogenic and to attack it. Brain damage, paralysis, and nearly 100 percent mortality resulted: Popov had created a biological weapon that in effect triggered rapid multiple sclerosis. (Popov's claims can be corroborated: in recent years, scientists researching treatments for MS have employed similar methods on test animals with similar results.)

When I asked about the prospects for creating bioweapons through synthetic biology, Popov mentioned the polio virus synthesized in 2002. "Very prominent people like [Anthony] Fauci at the NIH said, 'Now we know it can be done.'" Popov paused. "You know, that's…naïve. In 1981, I described how to carry out a project to synthesize small but biologically active viruses. Nobody at Biopreparat had even a little doubt it could be done. We had no DNA synthesizers then. I had 50 people doing DNA synthesis manually, step by step. One step was about three hours, where today, with the synthesizer, it could be a few minutes—it could be less than a minute. Nevertheless, already the idea was that we would produce one virus a month."

Effectively, Popov said, Biopreparat had few restrictions on manpower. "If you wanted a hundred people involved, it was a hundred. If a thousand, a thousand." It is a startling picture: an industrial program that consumed tons of chemicals and marshalled large numbers of biologists to construct, over months, a few hundred bases of a gene that coded for a single protein.

Though some dismiss Biopreparat's pioneering efforts because the Russians relied on technology that is now antiquated, this is what makes them a good guide to what could be done today with cheap, widely available biotechnology. Splicing into pathogens synthesized mammalian genes coding for the short chains of amino acids called peptides (that is, genes just a few hundred bases long) was handily within reach of Biopreparat's DNA synthesis capabilities. Efforts on this scale are easily reproducible with today's tools.

What the Russians Did

The Soviet bioweapons program was vast and labyrinthine; not even Ken Alibek, its top scientific manager, knew everything. In assessing the extent of its accomplishment—and thus the danger posed by small groups armed with modern technology—we are to some degree dependent on Serguei Popov's version of things. Since his claims are so controversial, a question must be answered: Many (perhaps most) people would prefer to believe that Popov is lying. Is he?

The Russians' achievements tell us what is possible. At least some of what the Soviet bioweaponeers did with difficulty and expense can now be done easily and cheaply. And *all* of what they accomplished can be duplicated with time and money.

Popov's affiliation with Alibek is a strike against him at the U.S. Army Medical Research Institute of Infectious Diseases (Usamriid) at Fort Detrick, MD, where Biopreparat's former top scientist has his critics. Alibek, one knowledgeable person told me, effectively "entered the storytelling business when he came to America." Alibek's critics charge that because he received consulting fees while briefing U.S. scientists and officials, he exaggerated Soviet bioweaponeering achievements. In particular, some critics reject Alibek's claims that the U.S.S.R. had combined Ebola and other viruses—in order to create what Alibek calls "chimeras." The necessary technology, they insist, didn't yet exist. When I interviewed Alibek in 2003, however, he was adamant that Biopreparat *had* weaponized Ebola.

Alibek and Popov obviously have an interest in talking up Russia's bioweapons. But neither I, nor others with whom I've compared notes, have ever caught Popov in a false statement. One must listen to him carefully, however. Regarding Ebola chimeras, he told me when I first interviewed him in 2003, "You can speculate about a plague-Ebola combination. I know that those who ran the Soviet bioweapons program

studied that possibility. I can talk with certainty about a synthesis of plague and Venezuelan equine encephalitis, because I knew the guy who did that." Popov then described a Soviet strategy for hiding deadly viral genes inside some milder bacterium's genome, so that medical treatment of a victim's initial symptoms from one microbe would trigger a second microbe's growth. "The first symptom could be plague, and a victim's fever would get treated with something as simple as tetracycline. That tetracycline would itself be the factor inducing expression of a second set of genes, which could be a whole virus or a combination of viral genes."

In short, Popov indicated that a plague-Ebola combination was theoretically possible and that Soviet scientists had studied that possibility. Next, he made another turn of the screw: Biopreparat had researched recombinants that would effectively turn their victims into walking Ebola bombs. I had asked Popov for a picture of some worst-case scenarios, so I cannot complain that he was misleading me—but the Russians almost certainly never created the plague-Ebola combination.

One further testimonial to Popov: the man himself is all of a piece. Recalling his youth in Siberia, he told me, "I believed in the future, the whole idea of socialism, equity, and social justice. I was deeply afraid of the United States, the aggressive American military, capitalism—all that was deeply scary." He added, "It's difficult to communicate how people in the Soviet Union thought then about themselves and how much excitement we young people had about science." Biological-weapons development was a profession into which Popov was recruited in his 20s and which informed his life and thinking for years. To ask him questions about biological weapons is to elicit a cascade of analysis of the specific cell-signaling pathways and receptors that could be targeted to induce particular effects, and how that targeting might be achieved via the genetic manipulation of pathogens. Popov is not explicable unless he is what he claims to be.

Popov's research in Russia is powerfully suggestive of the strangeness of recombinant biological weapons. Because genetics and molecular biology were banned as "bourgeois science" in the U.S.S.R. until the early 1960s, Popov was among the first generation of Soviet university graduates to grow up with the new biology. When he first joined Vector, or the State Research Center of Virology and Biotechnology, Biopreparat's premier viral research facility near Novosibirsk, he didn't immediately understand that he had entered the bioweaponeering business. "Nobody talked about biological weapons," he told me. "Simply, it was supposed to be peaceful research, which would transition from pure science to a new microbiological industry." Matters proceeded, however. "Your boss says, 'We'd like you to join a very interesting project.' If you say no, that's the end of your career. Since I was ambitious then, I went further and further. Initially, I had a dozen people working under me. But the next year I got the whole department of fifty people."

Access codes were stamped on Serguei Popov's Biopreparat ID.

In 1979, Popov received orders to start research in which small, synthesized genes coding for production of beta-endorphins—the opioid neurotransmitters produced in response to pain, exercise, and other stress—were to be spliced into viruses. Ostensibly, this work aimed to enhance the pathogens' virulence. Popov shrugged, recalling this. "How could we increase virulence with endorphins? Still, if some general tells you, you do it." Popov noted that the particular general who ordered the project, Igor Ashmarin, was also a molecular biologist and, later, an academician on Moscow State University's biology faculty. "Ashmarin's project sounded unrealistic but not impossible. The peptides he suggested were short, and we knew how to synthesize the DNA."

COURTESY OF SERGUEI POPOV

Peptides, such as beta-endorphins, are the constituent parts of proteins and are no longer than 50 amino acids. Nature exploits their compactness in contexts where cell signaling takes place often and rapidly—for instance, in the central nervous system, where peptides serve as neurotransmitters. With 10 to 20 times fewer amino acids than an average protein, peptides are produced by correspondingly smaller DNA sequences, which made them good candidates for synthesis using Biopreparat's limited means. Popov set a research team to splicing synthetic endorphin-expressing genes into various viruses, then infecting test animals.

Yet the animals were unaffected. "We had huge pressure to produce these more lethal weapons," Popov said. "I was in charge of new projects. Often, it was my responsibility to develop the project, and if I couldn't, that would be my problem. I couldn't say, 'No, I won't do it.' Because, then, what about your children? What about your family?" To appease their military bosses, Popov and his researchers shifted to peptides other than beta-endorphins and discovered that, indeed, microbes bearing genes that expressed myelin protein could provoke animals' immune systems to attack their own nervous systems. While the Vector team used this technique to increase the virulence of vaccinia, with the ultimate goal of applying it to smallpox, Popov was sent to Obolensk to develop the same approach with bacteria. Still, he told me, "We now know that if we'd continued the original approach with beta-endorphins, we would have seen their effect."

This vision of subtle bioweapons that modified behavior by targeting the nervous system—inducing effects like temporary schizophrenia, memory loss, heightened aggression, immobilizing depression, or fear—was irresistibly attractive to Biopreparat's senior military scientists. After Popov's defection, the research continued. In 1993 and 1994, two papers, copublished in Russian science journals by Ashmarin and some of Popov's former colleagues, described experiments in which vaccines of recombinant tularemia successfully produced beta-endorphins in test animals and thereby increased their thresholds of pain sensitivity. These apparently small claims amount to a proof of concept: bioweapons can be created that target the central nervous system, changing perception and behavior.

I asked Popov whether bioweaponeers could design pathogens that induced the type of effects usually associated with psychopharmaceuticals.

"Essentially, a pathogen is only a vehicle," Popov replied. "Those vehicles are available—a huge number of pathogens you could use for different jobs. If the drug is a peptide like endorphin, that's simple. If you're talking about triggering the release of serotonin and dopamine—absolutely possible. To cause amnesia, schizophrenia—yes, it's theoretically possible with pathogens. If you talk about pacification of a subject population—yes, it's possible. The beta-endorphin was proposed as potentially a pacification agent. For more complex chemicals, you'd need the whole biological pathways that produce them. Constructing those would be enormously difficult. But any drug stimulates specific receptors, and that is doable in different ways. So instead of producing the drug, you induce the consequences. Pathogens could do that, in principle."

Psychotropic recombinant pathogens may sound science fictional, but sober biologists support Popov's analysis. Harvard University professor of molecular biology Matthew Meselson is, with Frank Stahl, responsible for the historic Meselson-Stahl experiment of 1957, which proved that DNA replicated semiconservatively, as Watson and Crick had proposed. Meselson has devoted much effort to preventing biological and chemical weapons. In 2001, warning that biotechnology's advance was transforming the possibilities of bioweaponeering, he wrote in the *New York Review of Books*, "As our ability to modify life processes continues its rapid advance, we will not only be able to devise additional ways to destroy life but will also become able to manipulate it—including the fundamental biological processes of cognition, development, reproduction, and inheritance."

I asked Meselson if he still stood by this. "Yes," he said. After telling him of Popov's accounts of Russian efforts to engineer neuromodulating pathogens, I said I was dubious that biological weapons could achieve such specific effects. "Why?" Meselson bluntly asked. He didn't believe such agents had been created *yet*—but they were possible.

No one knows when such hypothetical weapons will be real. But since Popov left Russia, the range and power of biotechnological tools for manipulating genetic control circuits have grown. A burgeoning revolution in "targeting specificity" (targeting is the process of engineering molecules to recognize and bind to particular types of cells) is creating new opportunities in pharmaceuticals; simultaneously, it is advancing the prospects for chemical and biological weapons. Current research is investigating agents that target the distinct biochemical pathways in the central nervous system and that could render people sedate, calm, or otherwise incapacitated. All that targeting specificity could, in principle, also be applied to biological weapons.

The disturbing scope of the resulting possibilities was alluded to by George Poste, former chief scientist at SmithKline Beecham and the sometime chairman of a task force on bioterrorism at the U.S. Defense Department, in a speech he gave to the National Academies and the Center for Strategic and International Studies in Washington, DC, in January 2003. According to the transcript of the speech, Poste recalled that at a recent biotech conference he had attended a presentation on agents that augment memory: "A series of aged rats were paraded with augmented memory functions…. And some very elegant structural chemistry was placed onto the board…. Then with the most casual wave of the hand the

presenter said, 'Of course, modification of the methyl group at C7 completely eliminates memory. Next slide, please.'"

Basement Biotech

The age of bioweaponeering is just dawning: almost all of the field's potential development lies ahead.

The recent report by the National Academies described many unpleasant scenarios: in addition to psychotropic pathogens, the academicians imagine the misuse of "RNA interference" to perturb gene expression, of nanotechnology to deliver toxins, and of viruses to deliver antibodies that could target ethnic groups.

This last is by no means ridiculous. Microbiologist Mark Wheelis at the University of California, Davis, who works with the Washington-based Center for Arms Control and Non-Proliferation, notes in an article for *Arms Control Today*, "Engineering an ethnic-specific weapon targeting humans is...difficult, as human genetic variability is very high both within and between ethnic groups...but there is no reason to believe that it will not eventually be possible."

But commentators have focused on speculative perils for decades. While the threats they describe are plausible, dire forecasts have become a ritual—a way to avoid more immediate problems. Already, in 2006, much could be done.

Popov's myelin autoimmunity weapon could be replicated by bioterrorists. It would be no easy feat: while the technological requirements are relatively slight, the scientific knowledge required is considerable. At the very least, terrorists would have to employ a real scientist as well as lab technicians trained to manage DNA synthesizers and tend pathogens. They would also have to find some way to disperse their pathogens. The Soviet Union "weaponized" biological agents by transforming them into fine aerosols that could be sprayed over large areas. This presents engineering problems of an industrial kind, possibly beyond the ability of any substate actor. But bioterrorists might be willing to infect themselves and walk through crowded airports and train stations: their coughs and sniffles would be the bombs of *their* terror campaign.

Difficult as it may still be, garage-lab bioengineering is getting easier every year. In the vanguard of those who are calling attention to biotechnology's potential for abuse is George Church, Harvard Medical School Professor of Genetics. It was Church who announced in December 2004 that his research team had developed a new high-throughput synthesizer capable of constructing in one pass a DNA molecule 14,500 bases long.

Church says his DNA synthesizer could make vaccine and pharmaceutical production vastly more efficient. But it could also enable the manufacture of the genomes of all the viruses on the U.S. government's "select agents" list of bioweapons. Church fears that starting with only the constituent chemical reagents and the DNA sequence of one of the select agents, someone with sufficient knowledge might construct a lethal virus. The smallpox virus variola, for instance, is approximately 186,000 bases long—just 13 smaller DNA molecules to be synthesized with Church's technology and bound together into one viral genome. To generate infectious particles, the synthetic variola would then need to be "booted" into operation in a host cell. None of this is trivial; nevertheless, with the requisite knowledge, it could be done.

I suggested to Church that someone with the requisite knowledge might not need his cutting-edge technology to do harm. A secondhand machine could be purchased from a website like eBay or LabX.com for around $5,000. Alternatively, the components—mostly off-the-shelf electronics and plumbing—could be assembled with a little more effort for a similar cost. Construction of a DNA synthesizer in this fashion would be undetectable by intelligence agencies.

> "I was in charge of new projects. Often, it was my responsibility to develop the project, and if I couldn't, that would be my problem. I couldn't say, 'No, I won't do it.' Because, then, what about your children? What about your family?"

The older-generation machine would construct only oligonucleotides, which would then have to be stitched together to function as a complete gene, so only small genes could be synthesized. But small genes can be used to kill people.

"People have trouble maintaining the necessary ultrapure approach even with commercial devices—but you definitely could do some things," Church acknowledged.

What things? Again, Serguei Popov's experience at Biopreparat is instructive. In 1981, Popov was ordered by Lev Sandakhchiev, Vector's chief, to synthesize fragments of smallpox. "I was against this project," Popov told me. "I thought it was an extremely blunt, stupid approach." It amounted to a pointlessly difficult stunt, he explained, to impress the Soviet military; when his researchers acquired real smallpox samples in 1983, the program was suspended. A closely related program that Popov had started, however, continued after he departed Vector for Biopreparat's Oblensk facility in the mid-1980s. This project used the poxvirus vaccinia, the relatively harmless relative of variola used as a vac-

cine against smallpox. Not only was vaccinia—whose genome is very similar to variola's—a convenient experimental stand-in for smallpox, but its giant size (by viral standards) also made it a congenial candidate to carry extra genes. In short, it was a useful model for bioweapons. For at least a decade, therefore, a team of Biopreparat scientists systematically inserted into vaccinia a variety of genes that coded for certain toxins and for peptides that act as signaling mechanisms in the immune system. Though Popov had directed that the recombinant-vaccinia program should proceed through the genes coding for immune system–modulating peptides, he left before the researchers finished with the interleukin genes. But it would be surprising if the Vector researchers did not reach the gene for interleukin-4 (IL-4), an immune-system peptide that coaxes white blood cells to increase their production of antibodies and then releases them.

There is some evidence that the Russians discovered the effects of inserting the IL-4 gene into a poxvirus. Those effects are deadly. In 2001, Ian Ramshaw and a team of virologists from the Australian National University in Canberra spliced *IL-4* into ectromelia, a mousepox virus, and learned that the resulting recombinant mousepox triggered massive overproduction of the IL-4 peptide. Even the immune systems of mice vaccinated against mousepox could not control the growth of the virus: a 60 percent mortality rate resulted. Other experiments have confirmed the lethality of the recombinant pathogen. The American poxvirus expert Mark Buller, of Saint Louis University in Missouri, engineered various versions of the recombinant, one of which maintained the mousepox virus's full virulence while generating excessive interleukin-4. *All* the mice infected with this recombinant died. The BBC reported that when asked about the Australian experiment, Sandakhchiev, Vector's director, remarked, "Of course, this is not a surprise."

Because vaccinia is universally available, it is fortunate that a vaccinia-*IL-4* hybrid would not be an effective biological weapon: vaccinia has limited transmissibility between humans. Still, there are other poxviruses that *are* transmissible. Smallpox, the most infamous, is nearly impossible for aspiring bioterrorists to acquire. But another, varicella-zoster, or common chickenpox, is easily acquired and even more infectious than smallpox.

What would happen if bioterrorists spliced *IL-4* into chickenpox and released the hybrid into the general population? Perhaps nothing. Very often, the Soviet bioweaponeers successfully spliced new genes into pathogens, only to find that infected test animals showed no symptoms. One reason was that the genetically engineered microbes were often "environmentally unstable"—that is, they did not retain the added genes. Engineering recombinant pathogens can be ineffective for other reasons, too: the foreign gene might be expressed in the "wrong" organ. But according to several virologists with knowledge of biological weapons, the result of splicing *IL-4* into chickenpox might be to suppress the immune response to the disease. According to these virologists, the effect would be similar to what happens to cancer patients when they catch chickenpox. They often die—even when treated with antiviral therapies. For healthy children or adults, chickenpox is usually a superficial disease that mainly affects the skin; but depending on the immunosuppressive state of an infected cancer patient, chickenpox lesions can be slow to heal, and the viscera—that is, the lungs, the liver, and the central nervous system—become progressively diseased.

Bioterrorists could create a varicella-*IL-4* recombinant virus more easily than they could acquire or manufacture the pathogens that top the select-agents list. *IL-4* is one of the standard genes used in medical research; a plasmid of human *IL-4* could be ordered from one of the DNA synthesis jobbing companies and delivered via FedEx for $350. If our hypothetical bioterrorists were worried about detection, they might avoid the DNA synthesis companies altogether. Conveniently, without its junk DNA, *IL-4* is only about 462 base pairs long. It's possible to download *IL-4*'s genetic sequence from the Internet, use a basic synthesizer to construct it in five segments, and then assemble those segments "manually," as Popov's scientists did. The other principal tools needed would be a centrifuge—like the $5,000 DNA synthesizer, cheaply available via Internet sites—and a transfection kit, a small bottle filled with reagent that costs less than $200 and which would be necessary to introduce the *IL-4* gene into chickenpox. Finally, the terrorists would also require an incubator and the media in which to grow the resulting cells. The total costs, including the DNA synthesizer: probably less than $10,000.

Be Afraid. But of What?

In the public debate about how to defend ourselves against biological weapons, the advance of biotechnology has been little discussed. Instead, most biologists and security analysts have debated the merits and shortcomings of Project BioShield, the Bush administration's $5.6 billion plan to protect the U.S. population from biological, chemical, radiological, or nuclear attack. After last year's bioterrorism conference in DC, I called on Richard Ebright, whose Rutgers laboratory researches transcription initiation (the first step in gene expression), to hear why he so opposes the biodefense boom (in its current form) and why he doesn't worry about terrorists' synthesizing biological weapons.

"There are now more than 300 U.S. institutions with access to live bioweapons agents and 16,500 individuals approved to handle them," Ebright told me. While all of those people have undergone some form of background

check—to verify, for instance, that they aren't named on a terrorist watch list and aren't illegal aliens—it's also true, Ebright noted, that "Mohammed Atta would have passed those tests without difficulty."

Furthermore, Ebright told me, at the time of our interview, 97 percent of the researchers receiving funds from the National Institute of Allergy and Infectious Diseases to study bioweapon agents had never been funded for such work before. Few of them, therefore, had any prior experience handling these pathogens; multiple incidents of accidental release had occurred during the previous two years.

Slipshod handling of bioweapons-level pathogens is scary enough, I conceded. But isn't the proliferation of bioweaponeering expertise, I asked, more worrisome? After all, what reliable means do we have of determining whether somebody set out to be a molecular biologist with the aim of developing bioweapons?

"That's the most significant concern," Ebright agreed. "If al-Qaeda wished to carry out a bioweapons attack in the U.S., their simplest means of acquiring access to the materials and the knowledge would be to send individuals to train within programs involved in biodefense research." Ebright paused. "And today, every university and corporate press office is trumpeting its success in securing research funding as part of this biodefense expansion, describing exactly what's available and where."

As for the threat of next-generation bioweapons agents, Ebright was dismissive: "To make an antibiotic-resistant bacterial strain is frighteningly straightforward, within reach of anyone with access to the material and knowledge of how to grow it." However, he continued, further engineering—to increase virulence, to provide escape from vaccines, to increase environmental stability—requires considerable skill and a far greater investment of effort and time. "It's clearly possible to engineer next-generation enhanced pathogens, as the former Soviet Union did. That there's been no bioweapons attack in the United States except for the 2001 anthrax attacks—which bore the earmarks of a U.S. biodefense community insider—means *ipso facto* that no substate adversary of the U.S. has access to the basic means of carrying it out. If al-Qaeda had biological weapons, they would release them."

Milton Leitenberg, the arms control specialist, goes a step further: he says because substate groups have not used biological weapons in the past, they are unlikely to do so in the near future. Such arguments are common in security circles. Yet for many contemplating the onrush of the life sciences and biotechnology, they have limited persuasiveness.

I suggested to Ebright that synthetic biology offered low-hanging fruit for a knowledgeable bioterrorist. He granted that there were scenarios with sinister potential. He allowed that biotechnology could make BioShield, which focuses on conventional select agents such as smallpox, anthrax, and Ebola, less relevant. Still, he maintained, "a conventional bioweapons agent can potentially be massively disruptive in economic costs, fear, panic, and casualties. The need to go to the next level is outside the incentive structure of any substate organization."

Even those who are intimately involved with biodefense often support this view. For an insider's perspective, I contacted Jens Kuhn, the Harvard Medical School virologist. The German-born Kuhn has worked not only at Usamriid, and at the Centers for Disease Control in Atlanta, but also—uniquely for a Westerner—at Vector.

Kuhn, like Ebright, is no fan of how the biodefense boom is unfolding. "When I was at Usamriid, it exemplified how a biodefense facility should be," he told me. "That's why I'm worried—because the system worked, and the experts were concentrated at the right places, Fort Detrick and the CDC. Now this expertise gets diluted, which isn't smart."

Kuhn believes, nevertheless, that some kind of national biodefense program is needed. He just doesn't think we are preparing for the right things. "Everybody makes this connection with bioterrorism, anthrax attacks, and al-Qaeda. That's completely wrong." Kuhn recalled his time at Vector and that facility's grand scale. "When you look at what the Russians did, those kinds of huge state programs with billions of dollars flowing into very sophisticated research carried on over decades—they're the problem. If nation-states start a Manhattan Project to build the perfect biological weapon, we're in deep shit."

But doesn't modern biotechnology, I asked, allow small groups to do unprecedented things in garage laboratories?

Kuhn conceded, "There are a few things out there" with the potential to kill people. But weighing the probabilities, he saw the threat in these terms: "Definitely more biowarfare than bioterrorism. Definitely more the sophisticated bioweapons coming in the future than the stuff now. There's danger coming towards us and we're focusing on concerns like BioShield. I don't think that's the stuff that will save us."

Is Help on the Way?

The 21st century will see a biological revolution analogous to the industrial revolution of the 19th. But both its benefits and its threats will be more profound and more disruptive.

The near-term threat is that genes could be hacked outside of large laboratories. This means that terrorists could create recombinant biological weapons. But the leading edge of bioweapon research has always been the work of government labs. The longer-term threat is what it always has been: national militaries. Biotechnology will furnish *them* with weapons of unprecedented power and specificity. George Poste, in his 2003 speech to the National Academies, warned his audience that in coming decades the life

sciences would loom ever larger in national-security matters and international affairs. Poste noted, "If you actually look at the history of the assimilation of technological advance into the calculus of military affairs, you cannot find a historical precedent in which dramatic new technologies that redress military inferiority are not deployed."

Harvard's Matthew Meselson has said the same and added that a world in which the new biotechnology was deployed militarily "would be a world in which the very nature of conflict had radically changed. Therein could lie unprecedented opportunities for violence, coercion, repression, or subjugation." Meselson adds, "Governments might have the objective of controlling very large numbers of people. If you have a situation of permanent conflict, people begin contemplating things that the ordinary rules of conflict don't allow. They begin to view the enemy as subhuman. Eventually, this leads to viewing people in your own culture as tools."

COURTESY OF SERGUEI POPOV

In 1987, Biopreparat conducted a "pathogens class" at its research complex in Obolensk. Serguei Popov is in the back row, far right.

What measures could mitigate both the near and the more distant threats of bioweaponry? BioShield, as it is now constituted, will not protect us from genetically engineered pathogens. A number of radical solutions (like somehow boosting the human immune system through generic immunomodifiers) have been proposed, but even if pursued, they might take years or decades to develop.

More immediately, no one has a good idea about what should be done. Some scientists hope to arrest the spread of bioweapons knowledge. Rutgers's Richard Ebright wants to reverse what he believes to be counterproductive in the funding of biodefense. More dramatically, Harvard's George Church is calling for all DNA synthesizers to be registered internationally. "This wouldn't be like regulating guns, where you just give people a license and let them do whatever they want," he says. "Along with the license would come responsibilities for reporting." Furthermore, Church believes that just as all DNA synthesizers should be registered, so should any molecular biologists researching the select agents or the human immune system response to pathogens. "Nobody's forced to do research in those areas. If someone does, then they should be willing to have a very transparent, spotlighted research career," Church says.

But enactment of Church's proposals would represent an unprecedented regulation of science. Worse, not all nations would comply. For instance, Russian biologists, some of whom are known to have worked at Biopreparat, have reportedly trained molecular-biology students at the Pasteur Institute in Tehran.

More fundamentally, arresting the progress of biological-weapons research is probably impractical. Biological knowledge is all one, and therapies cannot be easily distinguished from weapons. For example, a general trend in biomedicine is to use viral vectors in gene therapy.

Robert Carlson, senior scientist in the Genomation Lab and the Microscale Life Sciences Center in the Department of Electrical Engineering at the University of Washington, believes there are two options. On the one hand, we can clamp down on biodefense research, stunting our ability to respond to biological threats. Alternatively, we can continue to push the boundaries of what is known about how pathogens can be manipulated—spreading expertise in building biological systems, for better and for worse, through experiments like Buller's assembly of a mousepox-*IL4* recombinant—so we are not at a mortal disadvantage. One day, we must hope, technology will suggest an answer.

Serguei Popov has lived with these questions longer than most. When I asked him what could be done, he told me, "I don't know what kind of behavior or scientific or political measures would guarantee that the new biology won't hurt us." But the vital first step, Popov said, was for scientists to overcome their reluctance to discuss biological weapons. "Public awareness is very important. I can't say it's a solution to this problem. Frankly, I don't see any solution right now. Yet first we have to be aware." TR

Mark Williams is a contributing writer to Technology Review.

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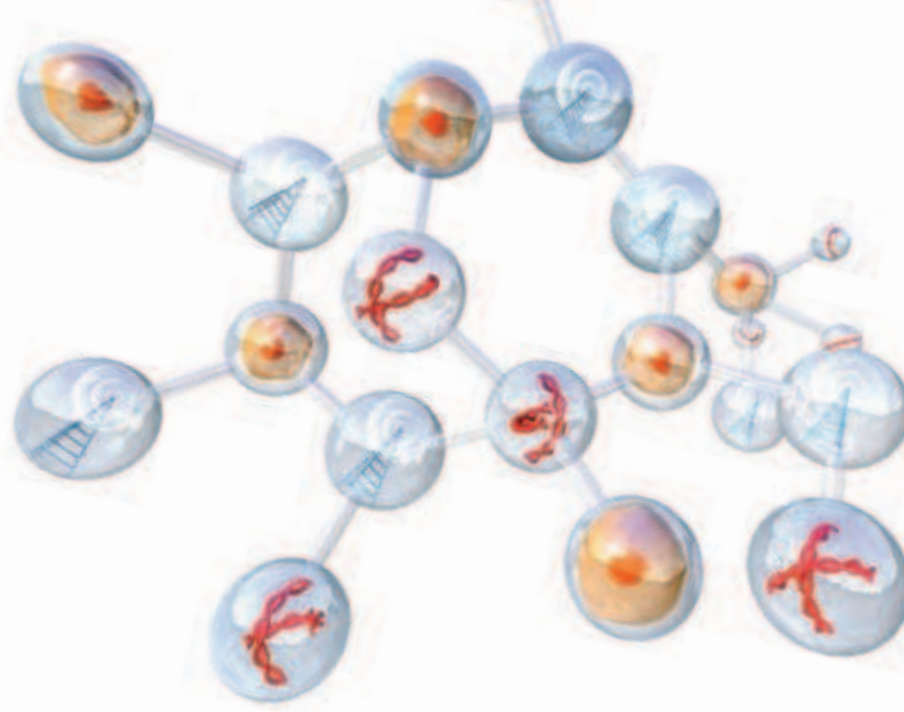


TechnologyReview

10 Emerging Technologies

EACH YEAR, *Technology Review* identifies 10 technologies that are worth keeping an eye on. This year's list spans a broad range of disciplines, from life sciences to nanotechnology to the Internet, but the technologies have one thing in common: they will soon have a significant impact on business, medicine, or culture. *Nanomedicine* and *nanobiomechanics* both illustrate nanotechnology's increasing contribution to the understanding and treatment of diseases. In biology, *epigenetics* is part of an exploding effort to understand the ways that chemical compounds can influence DNA, while *comparative interactomics* is a compelling example of how researchers are beginning to visualize the body's remarkable complexity. *Diffusion tensor imaging* is the most recent in a series of astonishing breakthroughs in imaging the brain. Meanwhile, *cognitive radio*, *pervasive wireless*, and *universal authentication* reflect the continuing struggle to keep the digital world accessible and secure. There is also controversy on the list: *nuclear reprogramming* describes the contentious hunt for an "ethical stem cell." Finally, some of the technologies, such as *stretchable silicon*, are just cool.

BRYAN CHRISTIE DESIGN

DRUG DISCOVERY

Comparative Interactomics

By creating maps of the body's complex molecular interactions, Trey Ideker is providing new ways to find drugs.

BIOMEDICAL RESEARCH THESE DAYS seems to be all about the "omes": genomes, proteomes, metabolomes. Beyond all these lies the mother of all omes—or maybe just the ome du jour: the interactome. Every cell hosts a vast array of interactions among genes, RNA, metabolites, and proteins. The impossibly complex map of all these interactions is, in the language of systems biology, the interactome.

Trey Ideker, a molecular biotechnologist by way of electrical engineering, has recently begun comparing what he calls the "circuitry" of the interactomes of different species. "It's really an incremental step in terms of the concepts, but it's a major leap forward in that we can gather and analyze completely new types of information to characterize biological systems," says Ideker, who runs the Laboratory for Integrative Network Biology at the University of California, San Diego. "I think it's going to be cool to map out the circuitry of all these cells."

Beyond the cool factor, Ideker and other leaders in the nascent field of interactomics hope that their work may help uncover new drugs, improve existing drugs by providing a better understanding of how they work, and even lead to computerized models of toxicity that could replace studies now conducted on animals. "Disease and drugs are about pathways," Ideker says.

Ideker made a big splash in the field in 2001 while still a graduate student with Leroy Hood at the Institute for Systems Biology in Seattle. In a paper for *Science*, Ideker, Hood, and coworkers described in startling detail how yeast cells use sugar. They presented a wiring-like diagram illustrating everything from the suite of genes involved, to the protein-protein interactions, to how perturbing the system altered different biochemical pathways. "His contribution was really special," says geneticist Marc Vidal of the Dana-Farber Cancer Institute in Boston, who introduced the concept that interactomes can be conserved between species. "He came up with one of the first good visualization tools."

Last November, Ideker's team turned heads by reporting in *Nature* that it had aggregated in one database all the available protein-protein interactomes of yeast, the fruit fly, the nematode worm, and the malaria-causing parasite *Plasmodium falciparum*. Though there's nothing particularly novel about comparing proteins across species, Ideker's lab is one of the few that has begun hunting for similarities and differences between the protein-protein *interactions* of widely different creatures. It turns out that the interactomes of yeast, fly, and worm include interactions called protein complexes that have some similarities between them. This conservation across species indicates that the interactions may serve some vital purpose. But *Plasmodium*, oddly, shares no protein complexes with worm or fly and only three with yeast.

OTHER PLAYERS
Comparative Interactomics

Researcher	Project
James Collins *Boston University*	Synthetic gene networks
Bernhard Palsson *University of California, San Diego*	Metabolic networks
Marc Vidal *Dana-Farber Cancer Institute, Boston, MA*	Comparison of interactomes among species

"For a while, we struggled to figure out what was going wrong with our analysis," says Ideker. After rechecking their data, Ideker and his team concluded that *Plasmodium* probably just had a somewhat different interactome.

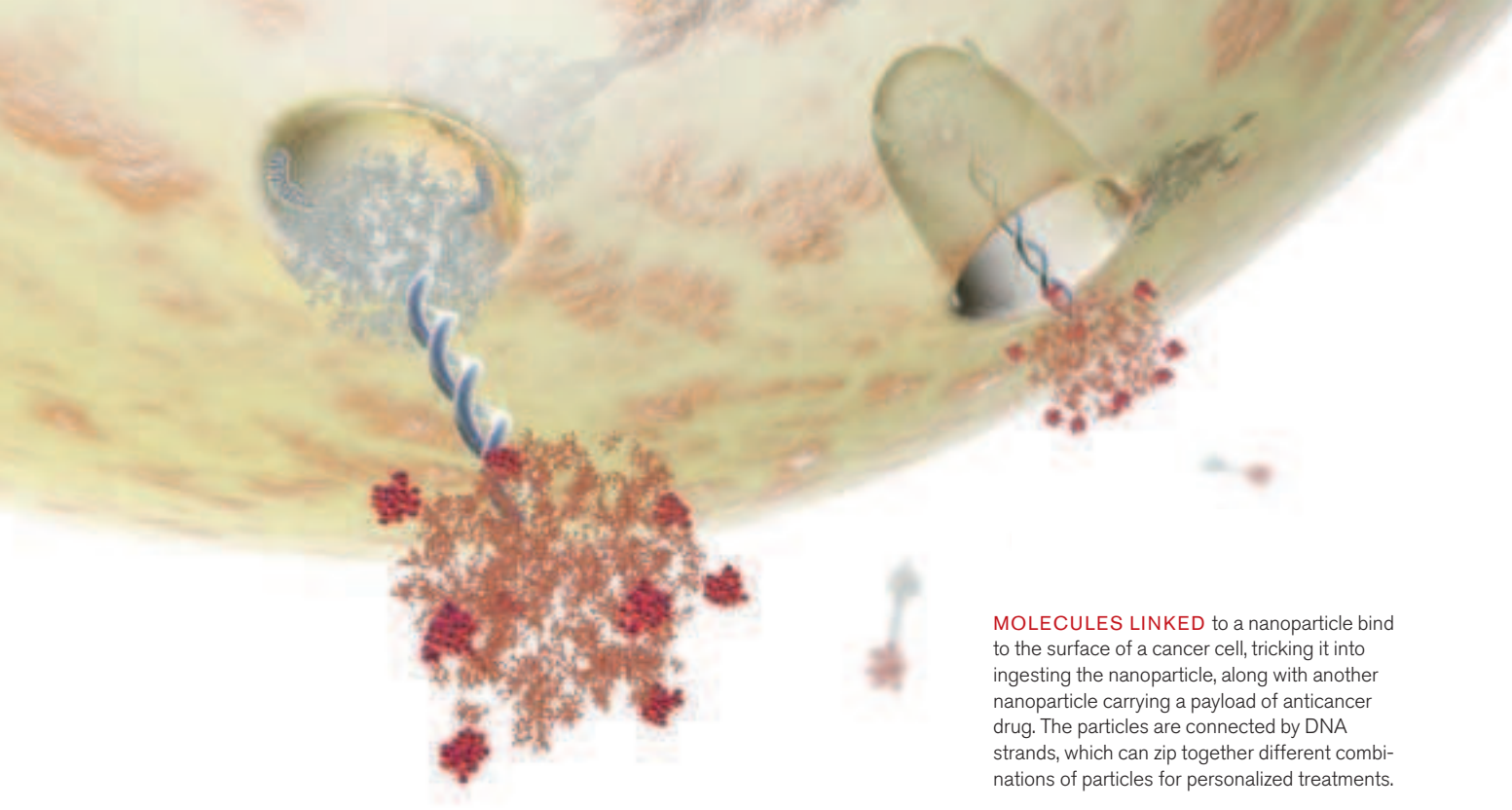
For pharmaceutical makers, the discovery of unique biological pathways, such as those found in the malaria parasite, suggests new drug targets. Theoretically, a drug that can interrupt such a pathway will have limited, if any, impact on circuits in human cells, reducing the likelihood of toxic side effects. Theoretically. In reality, pharmaceutical companies aren't exactly tripping over themselves to make new drugs for malaria—a disease that strikes mainly in poor countries. But the general idea has great promise, says Ideker, who now plans to compare the interactomes of different HIV strains to see whether any chinks in that virus's armor come to light.

George Church, who directs the Lipper Center for Computational Genetics at Harvard Medical School, has high respect for Ideker but adds another caveat: existing interactome data comes from fast, automated tests that simply aren't that accurate yet. "The way I divide the omes is by asking, Are these data permanent, or are they going to be replaced by something better?" says Church. Data on the DNA sequences of genomes, Church says, is permanent. But interactome data? "There's a 50-50 chance that this will be true or accepted in two years," says Church. "That's not Trey's fault. He's one of the people who is trying to make it more rigorous."

Ideker agrees that "there's a lot of noise in the system," but he says the continuing flood of interactome data is making what happens inside different cells ever more clear. "Within five years, we hope to take these interaction data and build models of cellular circuitry to predict actions of drugs before they're in human trials. That's the billion-dollar application." **JON COHEN**

GREGG SEGAL

Trey Ideker



MOLECULES LINKED to a nanoparticle bind to the surface of a cancer cell, tricking it into ingesting the nanoparticle, along with another nanoparticle carrying a payload of anticancer drug. The particles are connected by DNA strands, which can zip together different combinations of particles for personalized treatments.

THERAPEUTICS

Nanomedicine

James Baker designs nanoparticles to guide drugs directly into cancer cells, which could lead to far safer treatments.

THE TREATMENT BEGINS WITH AN injection of an unremarkable-looking clear fluid. Invisible inside, however, are particles precisely engineered to slip past barriers such as blood vessel walls, latch onto cancer cells, and trick the cells into engulfing them as if they were food. These Trojan particles flag the cells with a fluorescent dye and simultaneously destroy them with a drug.

Developed by University of Michigan physician and researcher James Baker, these multipurpose nanoparticles—which should be ready for patient trials later this year—are at the leading edge of a nanotechnology-based medical revolution. Such methodically designed nanoparticles have the potential to transfigure the diagnosis and treatment of not only cancer but virtually any disease. Already, researchers are working on inexpensive tests that could distinguish a case of the sniffles from the early symptoms of a bioterror attack, as well as treatments for disorders ranging from rheumatoid arthritis to cystic fibrosis. The molecular finesse of nanotechnology, Baker says, makes it possible to "find things like tumor cells or inflammatory cells and get into them and change them directly."

Cancer therapies may be the first nanomedicines to take off. Treatments that deliver drugs to the neighborhood of cancer cells in nanoscale capsules have recently become available for breast and ovarian cancers and for Kaposi's sarcoma. The next generation of treatments, not yet approved, improves the drugs by delivering them inside individual cancer cells. This generation also boasts multifunction particles such as Baker's; in experiments reported last June, Baker's particles slowed and even killed human tumors grown in mice far more efficiently than conventional chemotherapy.

"The field is dramatically expanding," says Piotr Grodzinski, program director of the National Cancer Institute's Alliance for Nanotechnology in Cancer. "It's not an evolutionary technology; it's a disruptive technology that can address the problems which former approaches couldn't."

The heart of Baker's approach is a highly branched molecule called a dendrimer. Each dendrimer has more than a hundred molecular "hooks" on its surface. To five or six of these, Baker connects folic-acid molecules. Because folic acid is a vitamin, most cells in the body have proteins on their surfaces that bind to it. But many cancer cells have significantly more of these receptors than normal cells. Baker links an anticancer drug to other branches of the dendrimer; when cancer cells ingest the folic acid, they consume the deadly drugs as well.

The approach is versatile. Baker has laden the dendrimers with molecules that glow under MRI scans, which can reveal the location of a cancer. And he can hook different targeting molecules and drugs to the dendrimers to treat a variety of tumors. He plans to begin human trials later this year, potentially on ovarian or head and neck cancer.

BRYAN CHRISTIE DESIGN

Mauro Ferrari, a professor of internal medicine, engineering, and materials science at Ohio State University, is hopeful about what Baker's work could mean for cancer patients. "What Jim is doing is very important," he says. "It is part of the second wave of approaches to targeted therapeutics, which I think will have tremendous acceleration of progress in the years to come."

To hasten development of nano-based therapies, the NCI alliance has committed $144.3 million to nanotech-related projects, funding seven centers of excellence for cancer nanotechnology and 12 projects to develop diagnostics and treatments, including Baker's.

Baker has already begun work on a modular system in which dendrimers adorned with different drugs, imaging agents, or cancer-targeting molecules could be "zipped together." Ultimately, doctors might be able to create personalized combinations of nanomedicines by simply mixing the contents of vials of dendrimers.

Such a system is at least 10 years away from routine use, but Baker's basic design could be approved for use in patients in as little as five years. That kind of rapid progress is a huge part of what excites doctors and researchers about nanotechnology's medical potential. "It will completely revolutionize large branches of medicine," says Ferrari. **KEVIN BULLIS**

OTHER PLAYERS
Nanomedicine

Researcher	Project
Raoul Kopelman *University of Michigan*	Nanoparticles for cancer imaging and therapy
Robert Langer *MIT*	Nanoparticle drug delivery for prostate cancer
Charles Lieber *Harvard University*	Nanowire devices for virus detection and cancer screening
Ralph Weissleder *Harvard University*	Magnetic nanoparticles for cancer imaging

HUMAN GENETICS

Epigenetics

Alexander Olek has developed tests to detect cancer early by measuring its subtle DNA changes.

SEQUENCING THE HUMAN GENOME was far from the last step in explaining human genetics. Researchers still need to figure out which of the 20,000-plus human genes are active in any one cell at a given moment. Chemical modifications can interfere with the machinery of protein manufacture, shutting genes down directly or making chromosomes hard to unwind. Such chemical interactions constitute a second order of genetics known as *epigenetics*.

In the last five years, researchers have developed the first practical tools for identifying epigenetic interactions, and German biochemist Alexander Olek is one of the trailblazers. In 1998, Olek founded Berlin-based Epigenomics to create a rapid and sensitive test for gene methylation, a common DNA modification linked to cancer. The company's forthcoming tests will determine not only whether a patient has a certain cancer but also, in some cases, the severity of the cancer and the likelihood that it will respond to a particular treatment. "Alex has opened up a whole new way of doing diagnostics," says Stephan Beck, a researcher at the Wellcome Trust Sanger Institute in Cambridge, England, and an epigenetics pioneer.

Methylation adds four atoms to cytosine, one of the four DNA "letters," or nucleotides. The body naturally uses methylation to turn genes on and off: the additional atoms block the proteins that transcribe genes. But when something goes awry, methylation can unleash a tumor by silencing a gene that normally keeps cell growth in check. Removing a gene's natural methylation can also render a cell can-

Alexander Olek

GUNTER KLOETZER/LAIF/REDUX

Heather Zheng

cerous by activating a gene that is typically "off" in a particular tissue.

The problem is that methylated genes are hard to recognize in their native state. But Olek says Epigenomics has developed a method to detect as little as three picograms of methylated DNA; it will spot as few as three cancer cells in a tissue sample.

To create a practical diagnostic test for a given cancer, Epigenomics compares several thousand genes from cancerous and healthy cells, identifying changes in the methylation of one or more genes that correlate with the disease. Ultimately, the test examines the methylation states of only the relevant genes. The researchers go even further through a sort of epigenetic archeology: by examining the DNA in tissues from past clinical trials, they can identify the epigenetic signals in the patients who responded best or worst to a given treatment.

Philip Avner, an epigenetics pioneer at the Pasteur Institute in Paris, says that Epigenomics' test is a powerful tool for accurately diagnosing and understanding cancers at their earliest stages. "If we can't prevent cancer, at least we can treat it better," says Avner.

Roche Diagnostics expects to bring Epigenomics' first product, a screening test for colon cancer, to market in 2008. The test is several times more likely to spot a tumor than the current test, which measures the amount of blood in a stool sample. And thanks to the sensitivity of its process, Epigenomics can detect the tiny amounts of methylated DNA such tumors shed into the bloodstream, so only a standard blood sample is required. The company is working on diagnostics for three more cancers: non-Hodgkin's lymphoma, breast cancer, and prostate cancer.

Olek believes that epigenetics could also have applications in helping explain how lifestyle affects the aging process. It might reveal, for example, why some individuals have a propensity toward diabetes or heart disease.

Olek's goal is a human-epigenome mapping project that would identify the full range of epigenetic variation possible in the human genome. Such a map, Olek believes, could reveal the missing links between genetics, disease, and the environment. Today, progress on the methylation catalogue is accelerating, thanks to Epigenomics and the Wellcome Trust Sanger Institute, which predict that the methylation status of 10 percent of human genes will be mapped by the end of this year. **PETER FAIRLEY**

OTHER PLAYERS
Epigenetics

Researcher	Project
Stephan Beck *Wellcome Trust Sanger Institute, Cambridge, England*	Epigenetics of the immune system
Joseph Bigley *OncoMethylome Sciences, Durham, NC*	Cancer diagnosis and drug development
Thomas Gingeras *Affymetrix, Santa Clara, CA*	Gene chips for epigenetics

WIRELESS

Cognitive Radio

To avoid future wireless traffic jams, Heather "Haitao" Zheng is finding ways to exploit unused radio spectrum.

GROWING NUMBERS OF PEOPLE ARE making a habit of toting their laptops into Starbuck's, ordering half-caf skim lattes, and plunking down in chairs to surf the Web wirelessly. That means more people are also getting used to being kicked off the Net as computers competing for bandwidth interfere with one another. It's a local effect—within 30 to 60 meters of a transceiver—but there's just no more space in the part of the radio spectrum designated for Wi-Fi.

Imagine, then, what happens as more devices go wireless—not just laptops, or cell phones and BlackBerrys, but sensor networks that monitor everything from temperature in office buildings to moisture in cornfields, radio frequency ID tags that track merchandise at the local Wal-Mart, devices that monitor nursing-home patients. All these gadgets have to share a finite—and increasingly crowded—amount of radio spectrum.

Heather Zheng, an assistant professor of computer science at the University of California, Santa Barbara, is working on ways to allow wireless devices to more efficiently share the airwaves. The problem, she says, is not a dearth of radio spectrum; it's the way that spectrum is used. The Federal Communications Commission in the United States, and its counterparts around the world, allocate the radio spectrum in swaths of frequency of varying widths. One band covers AM radio, another VHF television, still others cell phones, citizen's-band radio, pagers, and so on; now, just as wireless devices have begun proliferating, there's little left over to dole out. But as anyone who has twirled a radio dial knows, not every channel in every band is always in use. In fact, the FCC has determined that, in some locations or at some times of day, 70 percent of the allocated spectrum may be sitting idle, even though it's officially spoken for.

Zheng thinks the solution lies with cognitive radios, devices that figure out which frequencies are quiet and pick one or more over which to transmit and receive data. Without careful planning, however, certain bands could still end up jammed. Zheng's answer

GREGG SEGAL

is to teach cognitive radios to negotiate with other devices in their vicinity. In Zheng's scheme, the FCC-designated owner of the spectrum gets priority, but other devices can divvy up unused spectrum among themselves.

But negotiation between devices uses bandwidth in itself, so Zheng simplified the process. She selected a set of rules based on "game theory"—a type of mathematical modeling often used to find the optimal solutions to economics problems—and designed software that made the devices follow those rules. Instead of each radio's having to tell its neighbor what it's doing, it simply observes its neighbors to see if they are transmitting and makes its own decisions.

Zheng compares the scheme to a driver's reacting to what she sees other drivers doing. "If I'm in a traffic lane that is heavy, maybe it's time for me to shift to another lane that is not so busy," she says. When shifting lanes, however, a driver needs to follow rules that prevent her from bumping into others.

Zheng has demonstrated her approach in computer simulations and is working toward testing it on actual hardware. But putting spectrum-sharing theory into practice will take engineering work, from designing the right antennas to writing the software that will run the cognitive radios, Zheng acknowledges. "This is just a starting phase," she says.

Nonetheless, cognitive radios are already making headway in the real world. Intel has plans to build reconfigurable chips that will use software to analyze their environments and select the best protocols and frequencies for data transmission. The FCC has made special allowances so that new types of wireless networks can test these ideas on unused television channels, and the Institute of Electrical and Electronics Engineers, which sets many of the technical standards that continue to drive the Internet revolution, has begun considering cognitive-radio standards. It may be 10 years before all the issues get sorted out, Zheng says, but as the airwaves become more crowded, all wireless devices will need more-efficient ways to share the spectrum. **NEIL SAVAGE**

OTHER PLAYERS
Cognitive Radio

Researcher	Project
Bob Broderson *University of California, Berkeley*	Advanced communication algorithms and low-power devices
John Chapin *Vanu, Cambridge, MA*	Software-defined radios
Michael Honig *Northwestern University*	Pricing algorithm for spectrum sharing
Joseph Mitola III *Mitre, McLean, VA*	Cognitive radios
Adam Wolisz *Technical University of Berlin, Germany*	Protocols for communications networks

STEM CELLS

Nuclear Reprogramming

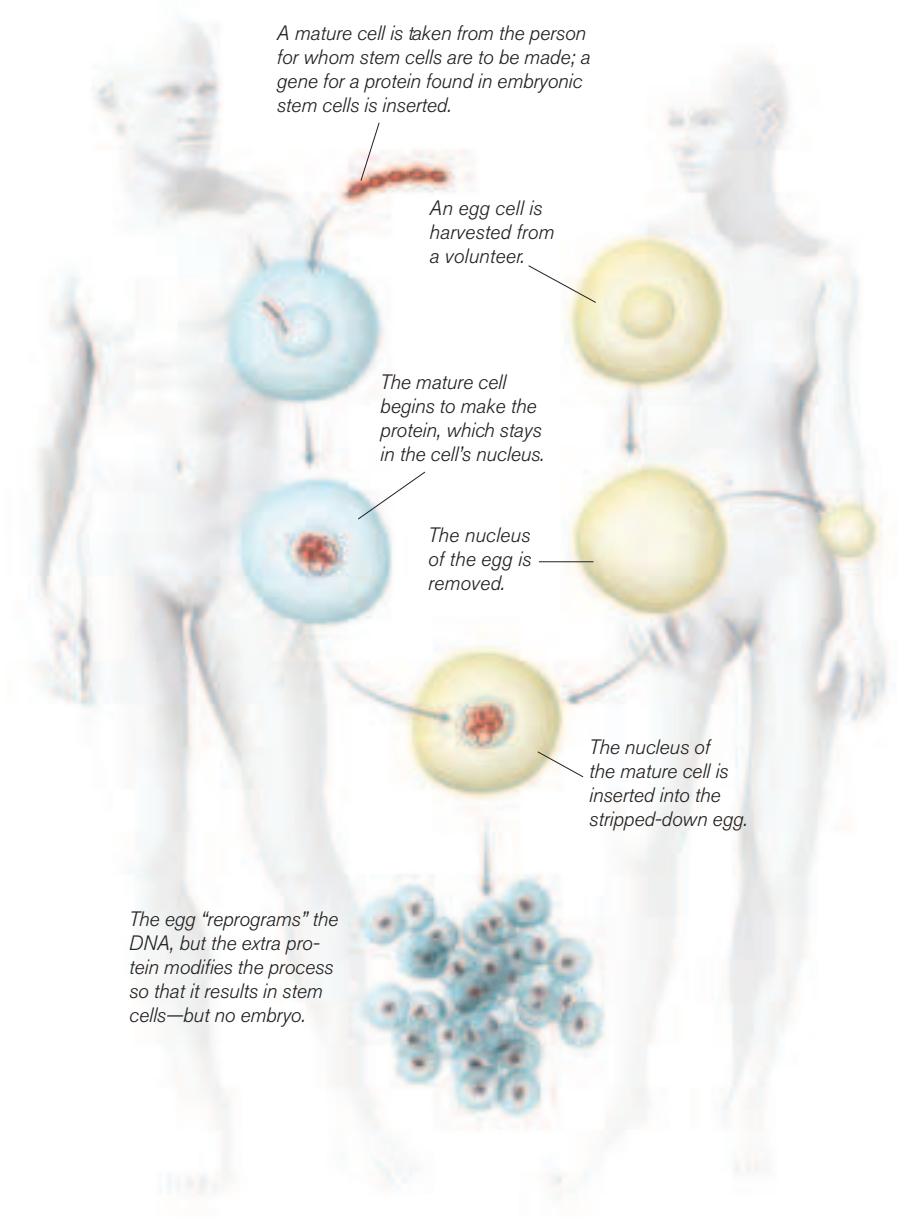
Hoping to resolve the embryonic-stem-cell debate, Markus Grompe envisions a more ethical way to derive the cells.

EMBRYONIC STEM CELLS MAY SPARK more vitriolic argument than any other topic in modern science. Conservative Christians aver that the cells' genesis, which requires destroying embryos, should make any research using them taboo. Many biologists believe that the cells will help unlock the secrets of devastating diseases such as Parkinson's and multiple sclerosis, providing benefits that far outweigh any perceived ethical harm.

Markus Grompe, director of the Oregon Stem Cell Center at Oregon Health and Science University in Portland, hopes to find a way around the debate by producing cloned cells that have all the properties of embryonic stem cells—but don't come from embryos. His plan involves a variation on the cloning procedure that produced Dolly the sheep. In the original procedure, scientists transferred the genetic material from an adult cell into an egg stripped of its own DNA. The egg's proteins reprogrammed the adult DNA, creating an embryo genetically identical to the adult donor. Grompe believes that by forcing the donor cell to produce a protein called nanog, which is normally found only in embryonic stem cells, he can alter the reprogramming process so that it never results in an embryo. Instead, it would yield a cell with many of the characteristics of an embryonic stem cell.

Grompe's work is part of a growing effort to find alternative ways to create cells with the versatility of embryonic stem cells. Many scientists hope to use proteins to directly reprogram, say, skin cells to behave like stem cells. Others think smaller molecules may do the trick; Scripps Research Institute chemist Peter Schultz has found a chemical that turns mouse muscle cells into cells able to form fat and bone cells. And Harvard University biologist Kevin Eggan believes it may be possible to create stem cells whose DNA matches a specific patient's by using existing stem cells stripped of their DNA to reprogram adult cells.

Meanwhile, researchers have tested methods for extracting stem cells without destroying viable embryos. Last fall, MIT biologist Rudolf Jaenisch and graduate student Alexander Meissner showed that by turning off a gene called *CDX2* in the nucleus of an adult cell



BRYAN CHRISTIE DESIGN

before transferring it into a nucleus-free egg cell, they could create a biological entity unable to develop into an embryo—but from which they could still derive normal embryonic stem cells.

Also last fall, researchers at Advanced Cell Technology in Worcester, MA, grew embryonic stem cells using a technique that resembles something called preimplantation genetic diagnosis (PGD). PGD is used to detect genetic abnormalities in embryos created through in vitro fertilization; doctors remove a single cell from an eight-cell embryo for testing. Lanza's team separated single cells from eight-cell mouse embryos, but instead of testing them, they put each in a separate petri dish, along with embryonic stem cells. Unidentified factors caused the single cells to divide and develop some of the characteristics of stem cells. When the remaining seven-cell embryos were implanted into female mice, they developed into normal mice.

Such methods, however, are unlikely to resolve the ethical debate because, in the eyes of some, they still endanger embryos. Grompe's approach holds out the promise of unraveling the moral dilemma. If it works, no embryo will have been produced—so no potential life will be harmed. As a result, some conservative ethicists have endorsed Grompe's proposal.

Whether it is actually a feasible way to harvest embryonic stem cells remains uncertain. Some are skeptical. "There's really no evidence it would work," says Jaenisch. "I doubt it would." But the experiments Grompe proposes, Jaenisch says, would still be scientifically valuable in helping explain how to reprogram cells to create stem cells. Harvard Stem Cell Institute scientist George Daley agrees. In fact, Daley's lab is also studying nanog's ability to reprogram adult cells.

Still, many biologists and bioethicists have mixed feelings about efforts to reprogram adult cells to become pluripotent. While they agree the research is important, they worry that framing it as a search for a stem cell compromise may slow funding—private and public—for embryonic-stem-cell research, hampering efforts to decipher or even cure diseases that affect thousands of desperate people. Such delays, they argue, are a greater moral wrong than the loss of cells that hold only the potential for life. Many ethicists—and the majority of Americans—seem to agree. "We've already decided as a society that it's perfectly okay to create and destroy embryos to help infertile couples to have babies. It seems incredible to me that we could say that that's a legitimate thing to do, but we can't do the same thing to help fight diseases that kill children," says David Magnus, director of the Stanford Center for Biomedical Ethics. **ERIKA JONIETZ**

OTHER PLAYERS
Nuclear Reprogramming

Researcher	Project
George Daley *Harvard Medical School*	Studying nanog's ability to reprogram nuclei
Kevin Eggan *Harvard University*	Reprogramming adult cells using stem cells
Rudolf Jaenisch *MIT*	Creating tailored stem cells using altered nuclear transfer (*CDX2*)

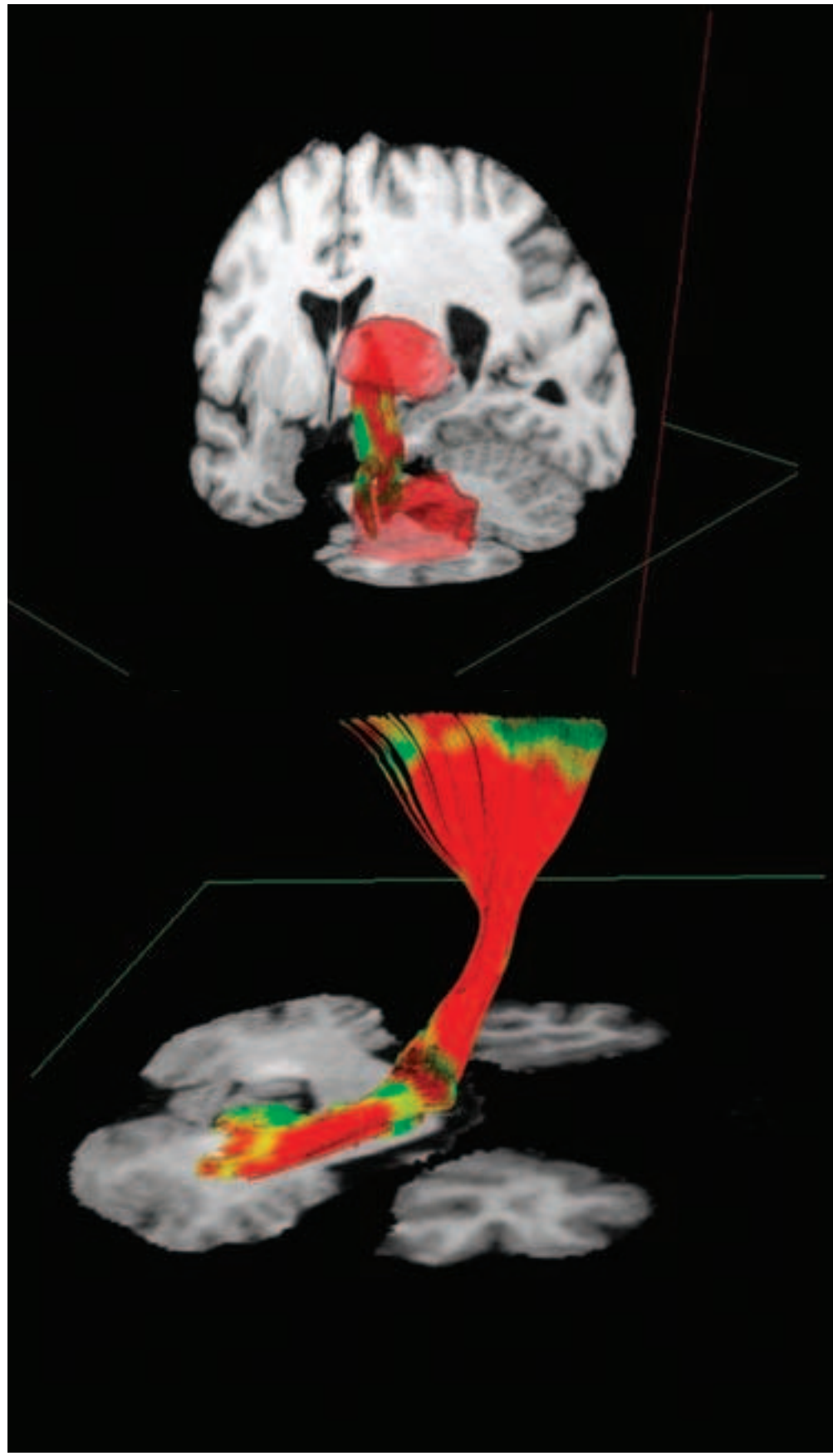
BRAIN IMAGING

Diffusion Tensor Imaging

Kelvin Lim is using a new brain-imaging method to understand schizophrenia.

FLIPPING THROUGH A PILE OF BRAIN scans, a neurologist or psychiatrist would be hard pressed to pick out the one that belonged to a schizophrenic. Although schizophrenics suffer from profound mental problems—hallucinated conversations and imagined conspiracies are the best known—their brains look more or less normal. This contradiction fascinated Kelvin Lim, a neuroscientist and psychiatrist at the University of Minnesota Medical School, when he began using imaging techniques such as magnetic resonance imaging (MRI) to study the schizophrenic brain in the early 1990s. Lim found subtle hints of brain structures gone awry, but to understand how these problems led to the strange symptoms of schizophrenia, he needed a closer look at the patients' neuroanatomy than standard scans could provide. Then, in 1996, a colleague told him about diffusion tensor imaging (DTI), a newly developed variation of MRI that allowed scientists to study the connections between different brain areas for the first time.

Lim has pioneered the use of DTI to understand psychiatric disease. He was one of the first to use the technology to uncover minute structural aberrations in the brains of schizophrenics. His group



DTI YIELDS images of nerve fiber tracts; different colors indicate the organization of the nerve fibers. Here, a tract originating at the cerebellum is superimposed on a structural-MRI image of a cross section of the brain.

has recently found that memory and cognitive problems associated with schizophrenia, major but undertreated aspects of the disease, are linked to flaws in nerve fibers near the hippocampus, a brain area crucial for learning and memory. "DTI allows us to examine the brain in ways we hadn't been able to before," says Lim.

Conventional imaging techniques, such as structural MRI, reveal major anatomical features of the brain—gray matter, which is made up of nerve cell bodies. But neuroscientists believe that some diseases may be rooted in subtle "wiring" problems involving axons, the long, thin tails of neurons that carry electrical signals and constitute the brain's white matter. With DTI, researchers can, for the first time, look at the complex network of nerve fibers connecting the different brain areas. Lim and his colleagues hope this sharper view of the brain will help better define neurological and psychiatric diseases and yield more-targeted treatments.

In DTI, radiologists use specific radio-frequency and magnetic field–gradient pulses to track the movement of water molecules in the brain. In most brain tissue, water molecules diffuse in all different directions. But they tend to diffuse along the length of axons, whose coating of white, fatty myelin holds them in. Scientists can create pictures of axons by analyzing the direction of water diffusion.

Following Lim's lead, other neuroscientists have begun using DTI to study a host of disorders, including addiction, epilepsy, traumatic brain injury, and various neurodegenerative diseases. For instance, DTI studies have shown that chronic alcoholism degrades the white-matter connections in the brain, which may explain the cognitive problems seen in heavy drinkers. Other DTI projects are examining how the neurological scars left by stroke, multiple sclerosis, and amyotrophic lateral sclerosis (better known as Lou Gehrig's disease) are linked to patients' disabilities.

Lim is pushing the technology even further by combining it with findings from other fields, such as genetics, to unravel the mysteries of neurological and psychiatric disorders. Lim's group has found, for instance, that healthy people with a genetic risk for developing Alzheimer's disease have tiny structural defects in specific parts of the brain that are not shared by noncarriers. How these defects might be linked to the neurological problems of Alzheimer's isn't clear, but the researchers are trying to find the connection.

Lim and others also continue to refine DTI itself, striving for an even closer look at the brain's microarchitecture. For example, current DTI techniques can easily image brain areas with large bundles of fibers all moving in the same direction, such as the corpus callosum, which connects the two hemispheres of the brain. But it has difficulty with areas such as the one where fibers leave the corpus callosum for other parts of the brain, which is a tangle of wires.

Researchers hope tools for studying white matter, like DTI, will help illuminate the mysteries of both healthy and diseased brains. Lim believes his own research into diseases like schizophrenia and Alzheimer's could yield better diagnostics within 10 to 20 years—providing new hope for the next generation of patients. **EMILY SINGER**

OTHER PLAYERS
DTI

Researcher	Project
Peter Basser *National Institute of Child Health and Human Development*	Development of higher-resolution diffusion imaging techniques
Aaron Field *University of Wisconsin-Madison*	Neurosurgery planning
Michael Moseley *Stanford University*	Assessment and early treatment of stroke

COURTESY OF VINCENT MAGNOTTA

INTERNET SECURITY

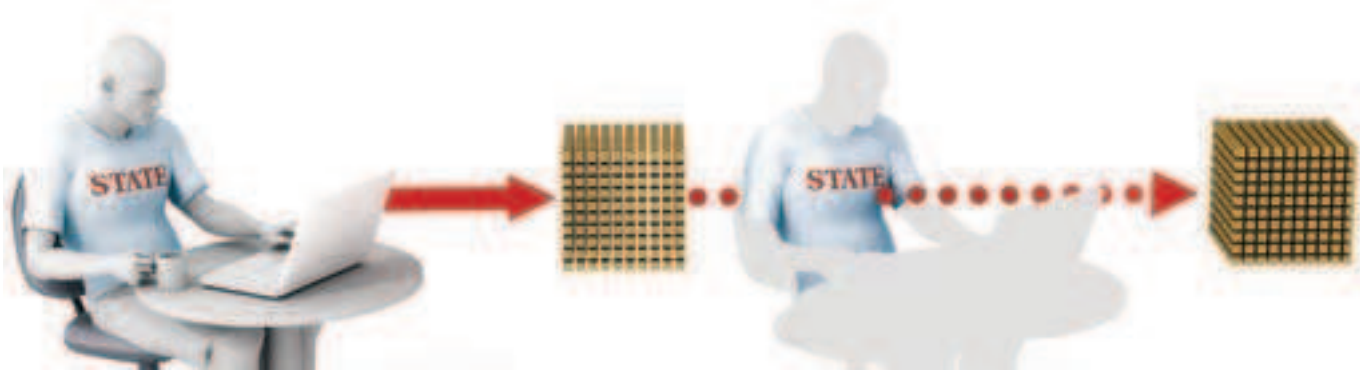
Universal Authentication

Leading the development of a privacy-protecting online ID system, Scott Cantor is hoping for a safer Internet.

IF YOU'RE LIKE MOST PEOPLE, YOU'VE established multiple user IDs and passwords on the Internet—for your employer or school, your e-mail accounts, online retailers, banks, and so forth. It's cumbersome and confusing, slowing down online interactions if only because it's so easy to forget the plethora of passwords. Worse, the diversity of authentication systems increases the chances that somewhere, your privacy will be compromised, or your identity will be stolen.

The balkanization of today's online identity-verifying systems is a big part of the Internet's fraud and security crisis. As Kim Cameron, Microsoft's architect of identity and access, puts it in his blog, "If we do nothing, we will face rapidly proliferating episodes of theft and deception that will cumulatively erode public trust in the Internet." Finding ways to bolster that trust is critically important to preserving the Internet as a useful, thriving medium, argues David D. Clark, an MIT computer scientist and the Internet's one-time chief protocol architect.

Scott Cantor, a senior systems developer at Ohio State University, thinks the answer may lie in Web "authentication systems" that allow users to



SECURITY WITH PRIVACY: Shibboleth software could create a far more trustworthy Internet by allowing a one-step login that carries through to many online organizations, confirming identity but preserving privacy. In this example, a student logs in to his university's site, then clicks through to a second university. Shibboleth confirms that the person is a student but doesn't give his name.

hop securely from one site to another after signing on just once. Such systems could protect both users' privacy and the online businesses and other institutions that offer Web-based services. Cantor led the technical development of Shibboleth, an open-standard authentication system used by universities and the research community, and his current project is to expand its reach. He has worked, not only to make the system function smoothly, but also to build bridges between it and parallel corporate efforts. "Scott is the rock star of the group," says Steven Carmody, an IT architect at Brown University who manages a Shibboleth project for Internet2, an Ann Arbor, MI–based research consortium that develops advanced Internet technologies for research laboratories and universities. "Scott's work has greatly simplified the management of these Internet-based relationships, while ensuring the required security and level of assurance for each transaction."

Shibboleth acts not only as an authentication system but also—counterintuitively—as a guardian of privacy. Say a student at Ohio State wishes to access Brown's online library. Ohio State securely holds her identifying information—name, age, campus affiliations, and so forth. She enters her user ID and password into a page on Ohio State's website. But when she clicks through to Brown, Shibboleth takes over. It delivers only the identifying information Brown really needs to know: the user is a registered Ohio State student.

While some U.S. universities have been using Shibboleth since 2003, adoption of the system grew rapidly in 2005. It's now used at 500-plus sites worldwide, including educational systems in Australia, Belgium, England, Finland, Denmark, Germany, Switzerland, and the Netherlands; even institutions in China are signing on. Also in late 2005, Internet2 announced Shibboleth's interoperability with a Microsoft security infrastructure called the Active Directory Federation Service.

Critically, the system is moving into the private sector, too. The science and medical division of research publishing conglomerate Reed Elsevier has begun granting university-based subscribers access to its online resources through Shibboleth, rather than requiring separate, Elsevier-specific logins. And Cantor has forged ties with the Liberty Alliance, a consortium of more than 150 companies and other institutions dedicated to creating shared identity and authentication systems. With Cantor's help, the alliance, which includes companies such as AOL, Bank of America, IBM, and Fidelity Investments, is basing the design of its authentication systems on a common standard known as SAML. The alliance, Cantor says, was "wrestling with lots of the same hard questions that we were, and we were starting to play in the same kind of territories. Now there is a common foundation.... we're trying to make it ubiquitous." With technical barriers overcome, the companies can now roll out systems as their business needs dictate.

Of course, Cantor is not the only researcher, nor Shibboleth the only technology, in the field of Internet authentication. In 1999, for instance, Microsoft launched its Passport system, which let Windows users access any participating website using their e-mail addresses and passwords. Passport, however, encountered a range of security and privacy problems.

But thanks to the efforts of the Shibboleth team and the Liberty Alliance, Web surfers could start accessing multiple sites with a single login in the next year or so, as companies begin rolling out interoperable authentication systems. **DAVID TALBOT**

BRYAN CHRISTIE DESIGN

OTHER PLAYERS

Universal Authentication

Researcher	Project
Stefan Brands *McGill University*	Cryptology, identity management, and authentication technologies
Kim Cameron *Microsoft, Redmond, WA*	"InfoCard" system to manage and employ a range of digital identity information
Robert Morgan *University of Washington*	"Person registry" that gathers identity data from source systems; scalable authentication infrastructure
Tony Nadalin *IBM, Armonk, NY*	Personal-identity software platform

MOLECULAR BIOLOGY

Nanobiomechanics

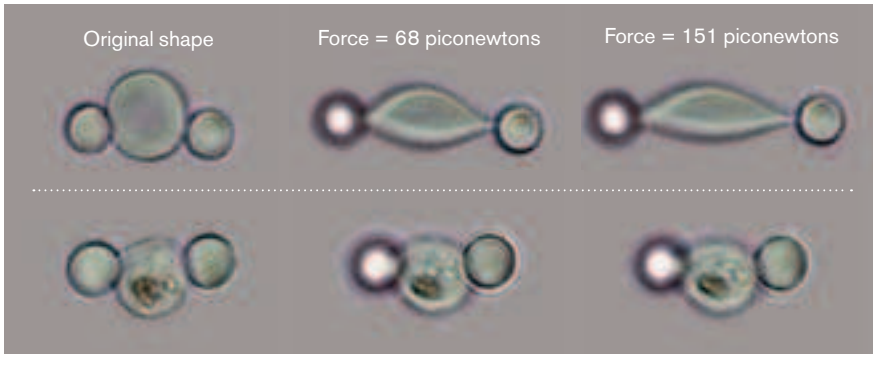
Measuring the tiny forces acting on cells, Subra Suresh believes, could produce fresh understanding of diseases.

MOST PEOPLE DON'T THINK OF THE human body as a machine, but Subra Suresh does. A materials scientist at MIT, Suresh measures the minute mechanical forces acting on our cells.

Medical researchers have long known that diseases can cause—or be caused by—physical changes in individual cells. For instance, invading parasites can distort or degrade blood cells, and heart failure can occur as muscle cells lose their ability to contract in the wake of a heart attack. Knowing the effect of forces as small as a piconewton—a trillionth of a newton—on a cell gives researchers a much finer view of the ways in which diseased cells differ from healthy ones.

Suresh spent much of his career making nanoscale measurements of materials such as the thin films used in microelectronic components. But since 2003, Suresh's laboratory has spent more and more time applying nanomeasurement techniques to living cells. He's now among a pioneering group of materials scientists who work closely with microbiologists and medical researchers to learn more about how our cells react to tiny forces and how their physical form is affected by disease. "We bring to the table expertise in measuring the strength of materials at the smallest of scales," says Suresh.

One of Suresh's recent studies measured mechanical differences between healthy red blood cells and cells infected with malaria parasites. Suresh and his collaborators knew that infected blood cells become more rigid, losing the ability to reduce their width from eight micrometers down to two or three micrometers, which they need to do to slip through capillaries. Rigid cells, on the other hand, can clog capillaries and cause cerebral hemorrhages. Though others had tried to determine exactly how rigid malarial cells become, Suresh's instruments were able to bring greater accuracy to the measurements. Using optical tweezers, which employ intensely focused laser light to exert a tiny force on objects attached to cells, Suresh and his collaborators showed that red blood cells infected with malaria become 10 times stiffer than healthy cells—three to four times stiffer than was previously estimated.



COURTESY OF SUBRA SURESH

OPTICAL TWEEZERS stretch a healthy red blood cell (top row), increasing the applied force slowly, by a matter of piconewtons. A cell in a late stage of malarial infection is stretched in a similar fashion (bottom row). The experiment illustrates how the infected cell becomes rigid, which prevents it from traveling easily through blood capillaries and helps cause the symptoms of malaria.

OTHER PLAYERS

Nanobiomechanics

Researcher	Project
Eduard Arzt, *Max Planck Institute, Stuttgart, Germany*	Structure and mobility of pancreatic cancer cells
Peter David and **Geneviève Milon**, *Pasteur Institute, Paris, France*	Parasite-host interaction; mechanics of the spleen
Ju Li, *Ohio State University*	Models of internal cellular structures
C. T. Lim and **Kevin Tan**, *National University of Singapore*	Red-blood-cell mechanics

Eduard Arzt, director of materials research at the Max Planck Institute in Stuttgart, Germany, says that Suresh's work is important because cell flexibility is a vital characteristic not only of malarial cells but also of metastasizing cancer cells. "Many of the mechanical concepts we've been using for a long time, like strength and elasticity, are also very important in biology," says Arzt.

Arzt and Suresh both caution that it's too early to say that understanding the mechanics of human cells will lead to more effective treatments. But what excites them and others in the field is the ability to measure the properties of cells with unprecedented precision. That excitement seems to be spreading: in October, Suresh helped inaugurate the Global Enterprise for Micro-Mechanics and Molecular Medicine, an international consortium that will use nanomeasurement tools to tackle major health problems, including malaria, sickle-cell anemia, cancer of the liver and pancreas, and cardiovascular disease. Suresh serves as the organization's founding director.

"We know mechanics plays a role in disease," says Suresh. "We hope it can be used to figure out treatments." If it can, the tiny field of nanomeasurement could have a huge impact on the future of medicine. **MICHAEL FITZGERALD**

NETWORKS

Pervasive Wireless

Can't all our wireless gadgets just get along? It's a question that Dipankar Raychaudhuri is trying to answer.

IN NEW BRUNSWICK, NJ, IS A LARGE, white room with an army of yellow boxes hanging from the ceiling. Eight hundred in all, the boxes are actually a unique grid of radios that lets researchers design and test ways to link mobile, radio-equipped computers in configurations that can change on the fly.

The ability to form such ad hoc networks, says Dipankar Raychaudhuri, director of the Rutgers University lab that houses the radios, will be critical to the advent of pervasive computing—in which everything from your car to your coffee cup "talks" to other devices in an attempt to make your life run more smoothly.

Wireless transactions already take place; anybody who speeds through tolls with an E-ZPass transmitter participates in them daily. But Raychaudhuri foresees a not-too-distant day when radio frequency identification (RFID) tags embedded in merchandise call your cell phone to alert you to sales, cars talk to each other to avoid collisions, and elderly people carry heart and blood-pressure monitors that can call a doctor during a medical emergency. Even mesh networks, collections of wireless devices that pass data one to another until it reaches a central computer, may need to be connected to pagers, cell phones, or other gadgets that employ diverse wireless protocols.

Hundreds of researchers at universities, large companies such as Microsoft, Intel, and Nortel, and small startups are developing embedded radio devices and sensors. But making computing truly pervasive entails tying these disparate pieces together, says Raychaudhuri, a professor of electrical and computer engineering at Rutgers. Finding ways to do that is what the radio test grid, which Raychaudhuri built with computer scientists Ivan Seskar and Max Ott, is for.

One problem the researchers are addressing is that different devices communicate using different radio standards: RFID tags use one set of standards, cell phones still others, and various Wi-Fi devices several versions of a third. Linking such devices into a pervasive network means providing them with a common protocol.

Take, for example, the issue of automotive safety. Enabling cars to communicate with each other could prevent crashes; in Raychaudhuri's vision, each car would have a Global Positioning System unit and send its exact location to nearby vehicles. But realizing that vision requires a protocol that allows the cars not only to communicate but also to decide how many other cars they should include in their networks and how close another car should be to be included. As programmers develop candidates for such a protocol, they try them out on the radio test bed. Each yellow box contains a computer and three different radios, two for handling the various Wi-Fi standards and one that uses either Bluetooth or ZigBee, short-range wireless protocols for personal electronics and for monitoring or control devices, respectively. The researchers configure the radios to mimic the situation they want to test and load their protocols to see, for instance, how long it takes each radio to detect neighbors and send data. "If I want cars not to collide, it cannot take 10 seconds to determine that a car is nearby," says Raychaudhuri. "It has to take a few microseconds."

The Rutgers radio grid is the first large-scale shared research facility that researchers can use to study multiple wireless devices and network technologies. "The sort of real-world complexity, dealing with real-world numbers that [the test bed] allows you to do, is something that really makes it quite unique," says Tod Sizer, director of the Wireless Technology Research Department at Lucent Technologies' Bell Labs.

Sizer's group is working with Raychaudhuri to build cognitive-radio boxes that can be programmed to employ a wide variety of wireless standards, such as RFID, Wi-Fi, or cellular-phone protocols.

While hordes of researchers are developing new networked devices, Raychaudhuri says it is the standardization of communications protocols that will make pervasive computing take off. In just five years, he believes, networks of embedded devices will be all around us. His aim is to reduce "friction" in daily life, eliminating lines, saving time in searching for objects, automating security checkpoints in airports, and the like. "You save 10 seconds here, two minutes there, but it's significant," he says. He claims that just a 2 percent reduction of friction in the world's economy could be worth hundreds of billions of dollars in productivity. "Each transaction is small, but the benefit to society is very large."

NEIL SAVAGE

OTHER PLAYERS

Pervasive Wireless

Researcher	Project
David Culler *University of California, Berkeley*	Operating systems and middleware for wireless sensors
Kazuo Imai *NTT DoCoMo, Tokyo, Japan*	Integrating cellular with other network technology
Lakshman Krishnamurthy and **Steven Conner** *Intel, Santa Clara, CA*	Wireless network architecture

STEVE MOORS

Dipankar Raychaudhuri

MICROELECTRONICS

Stretchable Silicon

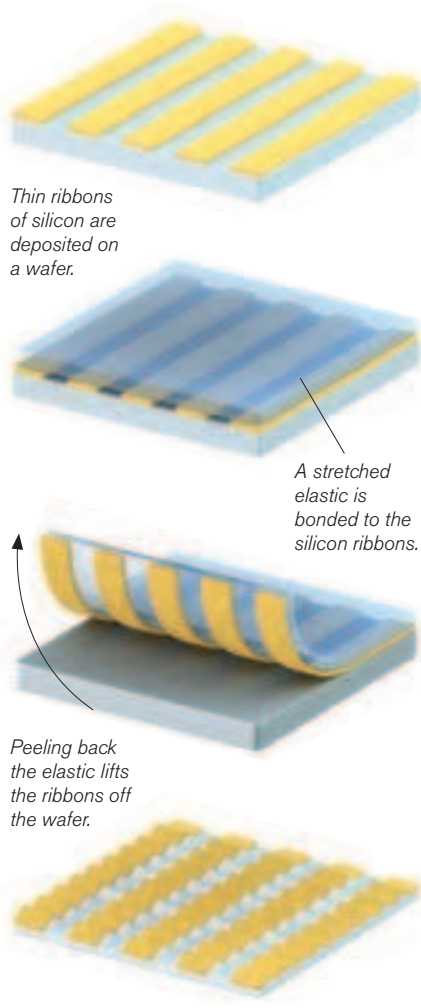
By teaching silicon new tricks, John Rogers is reinventing the way we use electronics.

THESE DAYS, MOST ELECTRONIC CIR-cuitry comes in the form of rigid chips, but devices thin and flexible enough to be rolled up like a newspaper are fast approaching. Already, "smart" credit cards carry bendable microchips, and companies such as Fujitsu, Lucent Technologies, and E Ink are developing "electronic paper"—thin, paperlike displays.

But most truly flexible circuits are made of organic semiconductors sprayed or stamped onto plastic sheets. Although useful for roll-up displays, organic semiconductors are just too slow for more intense computing tasks. For those jobs, you still need silicon or another high-speed inorganic semiconductor. So John Rogers, a materials scientist at the University of Illinois at Urbana-Champaign, found a way to stretch silicon.

If bendable is good, stretchable is even better, says Rogers, especially for high-performance conformable circuits of the sort needed for so-called smart clothes or body armor. "You don't comfortably wear a sheet of plastic," he says. The potential applications of circuitry made from Roger's stretchable silicon are vast. It could be used in surgeons' gloves to create sensors that would read chemical levels in the blood and alert a surgeon to a problem, without impairing the sense of touch. It could allow a prosthetic limb to use pressure or temperature cues to change its shape.

What makes Rogers's work particularly impressive is that he works with single-crystal silicon, the same type of silicon found in microprocessors. Like any other single crystal, single-crystal silicon doesn't naturally stretch. Indeed, in order for it even to bend, it must be prepared as an ultrathin layer only a few hundred nanometers thick on a bendable surface. Rogers exploits the flexibility of thin silicon, but instead of attaching it to plastic, he affixes it in narrow strips to a stretched-out, rubberlike polymer. When the stretched polymer snaps back, the silicon strips buckle but do not break, forming "waves" that are ready to stretch out again.



Releasing the tension on the elastic produces "waves" of silicon that can later be stretched out again as needed. Such flexible silicon could be used to make wearable electronics.

Rogers's team has fabricated diodes and transistors—the basic building blocks of electronic devices—on the thin ribbons of silicon before bonding them to the polymer; the wavy devices work just as well as conventional rigid versions, Rogers says. In theory, that means complete circuits of the sort found in computers and other electronics would also work properly when rippled.

Rogers isn't the first researcher to build stretchable electronics. A couple of years ago, Princeton University's Sigurd Wagner and colleagues began making stretchable circuits after inventing elastic-metal interconnects. Using the stretchable metal, Wagner's group connected together rigid "islands" of silicon transistors. Although the silicon itself couldn't stretch, the entire circuit could. But, Wagner notes, his technique isn't suited to making electrically demanding circuits such as those in a Pentium chip. "The big thing that John has done is use standard, high-performance silicon," says Wagner.

Going from simple diodes to the integrated circuits needed to make sensors and other useful microchips could take at least five years, says Rogers. In the meantime, his group is working to make silicon even more flexible. When the silicon is affixed to the rubbery surface in rows, it can stretch only in one direction. By changing the strips' geometry, Rogers hopes to make devices pliable enough to be folded up like a T-shirt. That kind of resilience could make silicon's future in electronics stretch out a whole lot further. **KATE GREENE**

OTHER PLAYERS

Stretchable Silicon

Researcher	Project
Stephanie Lacour *University of Cambridge, England*	Neuro-electronic prosthesis to repair damage to the nervous system
Takao Someya *University of Tokyo*	Large-area electronics based on organic transistors
Sigurd Wagner *Princeton University*	Electronic skin based on thin-film silicon

BRYAN CHRISTIE DESIGN

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The Fountain of Health

Antiaging researchers aren't likely to find ways to extend life anytime soon. But their work could provide a powerful approach to treating the many diseases of old age.

By David Rotman Illustration by Chris Buzelli

For the better part of two decades, Richard Weindruch, a professor of medicine at the University of Wisconsin–Madison, has fed half of a colony of 78 rhesus monkeys a diet adequate in nutrition but severely limited in calories—30 percent fewer calories than are fed to the control group. Scientists have known for nearly 70 years that such calorie restriction extends the life span of rodents, and Weindruch is determined to find out whether it can extend the life span of one of man's closest relatives, too.

It's too early to know the answer for certain. The monkeys in Weindruch's lab are only now growing elderly. And with 80 percent of them still alive, "there are too few deaths" to indicate whether the animals on the restricted diet will live longer, says Weindruch. But one thing is already clear: the monkeys on the restricted diet are healthier. Roughly twice as many of the monkeys in the control group have died from age-related diseases, and perhaps most dramatically, none of the animals on the restricted diet have developed diabetes, a leading cause of death in rhesus monkeys.

These encouraging, albeit preliminary, results are sure to cheer those few who have adopted severe calorie-restricted diets in hopes of living longer. But their real significance is the further evidence they provide that calorie restriction affects the molecular and genetic events that govern aging and the diseases of aging. Indeed, while calorie restriction remains impractical for all but the most determined dieters, it is providing an invaluable window on the molecular and cellular biology of disease resistance and the aging process.

Up until a decade or so ago, most biologists believed that the aging process was not only immensely complex but also inevitable. People aged, they assumed, much the way an old car does: eventually, everything just falls apart. Then in the early 1990s, Cynthia Kenyon, a young molecular biologist at the University of California, San Francisco, found that mutating a single gene, called *daf-2*, in worms doubled their life spans. Before the discovery, says Kenyon, "everyone thought aging just happened. To control aging, you had to fix everything, so it was impossible." Kenyon's research suggested a compelling alternative: that a relatively simple genetic network controlled the rate of aging.

The race to find the genetic fountain of youth was on. Within a few years, Leonard Guarente, a biologist at MIT, found that in yeast, another gene produced a similar dramatic increase in life span. Soon after, Guarente and his MIT coworkers made another startling discovery: the yeast antiaging gene, called *sir2*, required for its activity a common molecule that is involved in numerous metabolic reactions. Guarente, it seemed, had found a possible connection between an antiaging gene and diet. The gene, Guarente thought, might be responsible for the health benefits of calorie restriction; and indeed, the lab soon confirmed that calorie restriction in yeast had life-extending effects only when *sir2* was present.

Since the discovery of these and other antiaging genes in lower organisms, the scientific search for live-longer genes in people has, not surprisingly, garnered much publicity. Often lost in the excitement about the prospect of triple-digit birthdays, however, is a far more realistic and immediate implication of the research. While learning how to extend the life span of humans could take many decades, if it's even possible, researchers are already using insights gained from studies of aging and the effects of calorie restriction to search for new drugs to treat the numerous diseases tied to getting old.

The incidences of many illnesses, including cardiovascular disease, Alzheimer's, and cancer, rise nearly exponentially with age. And while we still don't know exactly why, we *do* know that calorie restriction—at least in test

animals—delays the onset of a broad swath of these age-related diseases. "It's something people are surprised to hear, because it really begs the question, how is that possible? There must be some common metabolic component. But no one really knows how all those diseases can be tied together," says Guarente. Nevertheless, some biologists hope that a drug that mimics the molecular effects of calorie restriction might also delay the onset of some or all of these diseases.

At least one company, Sirtris, a small but heavily funded startup in Cambridge, MA, believes it is close to finding such drugs. The company, which boasts an impressive group of prominent molecular biologists and geneticists on its scientific board, was cofounded by David Sinclair, a former postdoctoral researcher in Guarente's lab and now an associate professor at Harvard Medical School. Sirtris has come up with hundreds of molecules that activate the SIRT1 enzyme, which is produced by the mammalian homologue of *sir2*. (Seven different *SIRT* genes have been found in humans; these and their homologues in other species are collectively known as sirtuins.) If the company is on the right track—and Sirtris says potential drug candidates for treating diabetes and neurodegenerative diseases are expected to begin preliminary human tests over the next several years—the molecules could mimic the genetic effects of calorie restriction, offering its apparent health benefits without its drawbacks.

"It's known that calorie restriction greatly enhances the body's natural ability to fight diseases," says Sinclair.

The vital questions, he says, are what controls that process and whether we can develop drugs to target it. "We don't assume we know everything about it, but we do strongly believe that sirtuins are a major component in what could be a master regulatory system for human health."

Old Yeast

The identification of the life-extending effects of *sir2* in yeasts was no accident: Lenny Guarente had been searching for the causes of yeast aging for almost a decade when he and his MIT graduate students methodically zeroed in on the gene in 1999. It was an important finding, but its real significance became more apparent over the next year and a half.

First, Guarente and his students found the *sir2* gene in round worms. Since yeast and worms diverged evolutionarily billions of years ago, the presence of the same gene in both organisms suggested that it might be shared by other animals, including humans. Then came the bombshell. The expression of the *sir2* gene required the presence of another molecule, called NAD; as any biologist knew, NAD is involved in numerous metabolic reactions in many organisms. "This finding that *sir2* was NAD dependent meant to us that *sir2* could connect aging to metabolism and therefore to diet," says Guarente. "Once you see this activity, a child could point out, Maybe this would connect to caloric restriction."

Perhaps not most children, but other molecular biologists certainly saw the connection, and labs around the world soon began to puzzle out the effects of *sir2*. Scientists knew that calorie restriction could have an impact on disease. And now there was evidence of a strong link between *sir2* and calorie restriction. "If you put those together," says Guarente, "you can formulate a hypothesis that *sir2* genes will impact diseases of aging."

Amidst this flurry of research, however, it was a 2003 paper in the journal *Nature* by Sinclair and his collaborators that really caught the attention of those hoping to turn the science of sirtuins into drugs. Sinclair identified a class of common chemicals, called polyphenols, that activate sirtuins. The findings suggested it might be possible to develop small-molecule drugs that could interact with sirtuins and turn on their apparent beneficial effects.

Six months after the *Nature* paper, Sinclair cofounded Sirtris with Christoph Westphal, then a partner at Polaris Venture Partners, a Waltham, MA–based venture capital firm. [Disclosure: Polaris general partner Robert Metcalfe is on *Technology Review*'s board of directors.] Less than two years later, the startup has $45 million in venture financing and a series of drug candidates that activate *SIRT1* and other sirtuins in mammals. Within a few years, says Westphal, now Sirtris's CEO, the company hopes to begin testing the safety of the sirtuin activators in humans. "We're aiming to mimic calorie restriction with small molecules," says Westphal. "The great break for us was to find those small molecules."

Meanwhile, members of Sinclair's Harvard lab are busy conducting experiments on thousands of mice to prove the benefits of sirtuins in treating disease and aging. The mice are stacked in endless rows of small, clean cages packed into a series of locked rooms. Some of the mice, partly bald and stiff jointed, have been genetically engineered to age prematurely. Other cages hold animals genetically destined to get colon or prostate cancers, while yet other mice will develop neurological impairments of a kind associated with Alzheimer's disease. The researchers crossbreed these mice with animals genetically engineered to overexpress one of the sirtuin genes, then monitor how the offspring fare—whether the sirtuins fight off the diseases or prevent premature aging. Taken together, it is a massive effort to understand the role of sirtuins in mammals, with thousands of mice providing different pieces of the puzzle.

Given that the mice experiments are just a year old, and mice typically live for around three years, results are still preliminary. There is not yet any conclusive evidence, for one thing, that activating or overexpressing sirtuins increases the life span of the mice. But Sinclair says that the studies completed so far all show "that the diseases in the mice have been ameliorated."

Look Up

Elixir Pharmaceuticals and Sirtris have much in common. Both firms were founded to discover drugs for age-related diseases, using core technology built around antiaging genes. Both feature rosters of star antiaging researchers, with Elixir counting Guarente and Kenyon among its founders. Just a few miles apart, Elixir is at the edge of MIT's campus, while Sirtris is next to Harvard University.

But despite their similarities, the two companies seem to have radically different outlooks. At Elixir, which was founded in 1999, there is no evidence of the kind of youthful bravado that characterizes Sirtris. On the whiteboard in his small office, Peter DiStefano, Elixir's chief scientific officer, patiently and meticulously diagrams some of the metabolic pathways that the company is investigating. Some directly involve *SIRT1*; some don't. Arrows overlap in a complicated mesh; some arrows just wander off, pointing to unknown territory. DiStefano's point is clear: these molecular mechanisms are immensely complicated and still not completely understood.

"It's hard to say when we will get to a drug development candidate [based on sirtuins]. It's a little early," he says. He points to a small sign above his door, positioned so that it's the last thing you see as you leave the office. It reads, "The animal is always right." The challenge, says DiStefano, is translating the knowledge of mechanisms at the cellular

level into an understanding of effects on the whole organism. "You have to look at the entire animal. You can do a lot of cell-based experiments and see a lot of effects in cells, and those are absolutely important starting points, but you really need to glue it all together and figure out what happens at the organismal level."

Indeed, many questions about sirtuins remain unanswered. The genetic and molecular pathways involved in aging are complex, and their details remain much in dispute. Whether sirtuins are central to them is still, in fact, controversial: other labs are studying different genetic candidates for such a master role in the aging process. "It is still a very young field, and it suffers from lack of consensus," says Stephen Helfand, a professor of biology at Brown Medical School and discoverer of an aging gene called *indy* (for "I'm not dead yet") in fruit flies. "People don't agree on many things."

Even strong believers in sirtuins point out that scientists are just beginning to understand the genes' biology and their metabolic role. In particular, it's uncertain whether sirtuins act in mammals the same way they do in lower organisms. The experiments in which adding extra copies of *SIRT1* to mice failed to extend the life span of the animals are particularly troubling to some. Labs studying mice are also struggling to prove that the beneficial effects of calorie restriction require the activity of sirtuins—something that Guarente showed for yeast and Helfand for fruit flies but that hasn't been demonstrated in mammals.

Antiaging research and drug discovery efforts share a common premise; a few master genes are thought to regulate the body's ability to fight off diseases associated with aging *and* the extension of life span.

Risk Factor

At Elixir and Sirtris, there is little talk about slowing down the aging process. Rather, both companies are intensely focused on the discovery and development of drugs for various age-related diseases, such as type 2 diabetes. Sirtris's Westphal puts it bluntly: "I was never interested in a company that would try to prolong life. I was interested in a company that was going to use genes involved in diseases of aging and in finding an FDA-approved path to get those drugs approved for important disorders like diabetes and neurological disorders."

Nevertheless, antiaging research and drug discovery efforts like Sirtris's and Elixir's are closely linked and share a common premise; a few master genes are thought to regulate both the body's ability to fight off diseases associated with aging *and* the extension of life span. Though it is still a controversial hypothesis, Sinclair and Guarente believe that in times of adversity or stress—when food is scarce, for instance—sirtuins somehow marshal an organism's natural defenses. They argue that, among other things, activated *SIRT1* triggers changes in cells that mobilize repair mechanisms and increase energy production. It is, perhaps, these enhanced natural defense mechanisms that explain why animals on a calorie-restricted diet live longer and are healthier.

The idea that the genetic and molecular causes of aging and of many diseases are connected could provide a powerful new way of thinking about medicine, suggests Toren Finkel, a cardiologist at the National Heart, Lung, and Blood Institute in Bethesda, MD. Walk down the corridors of any hospital, he says, and you can't help but notice that many of the patients are elderly. "As cardiologists, we target what we view as causes of diseases—clearly involved risk factors like hypertension." While that approach is effective, he says, it has largely ignored the most obvious factor in many diseases: age.

"It is obvious....We get sicker as we get older," says Finkel. He says he's not sure whether that observation "is so obvious it is stupid, or so obvious it is profound." But either way, he says, new research explaining the genetic and molecular events behind the aging process is, for the first time, raising the possibility of treating a broad range of diseases by intervening in that process. "No one had really thought about controlling aging as a practical way to control these diseases," says Finkel. "But it could be a powerful way of treating patients."

Our understanding of why people grow old is still primitive, but researchers say the drug discovery effort can push ahead regardless. "We don't understand a damn thing about aging," admits Helfand. But he's quick to add that the health benefits of calorie restriction are well documented in many organisms. And that, he says, "is very exciting from a drug discovery perspective."

The goal is clear: the discovery of drugs that will delay the onset of many of our most devastating diseases, the kind of illnesses that frequently turn the golden years into years of chronic ill health. "Everybody associates caloric restriction with longevity and life span, but the effects on diseases are much more immediate and important," says Guarente. "If only we understood how [calorie restriction] works, such knowledge would guide us in drug development. We would have a drug that would favorably impact many of the common diseases." TR

David Rotman is editor of Technology Review.

Reviews

Books, artifacts, reports, products, objects

IN THE LIVING ROOM

Cinegames

Microsoft's new Xbox changes the state of play. **By Wade Roush**

It's October 1942. My company of British infantry has driven the Germans out of a small desert town—a choke point in the minefields laid down by Rommel's Afrika Korps south of El Alamein—and is now fending off a counterattack. I'm on a rooftop sighting German tanks through my binoculars and shouting coördinates to the gunner at the 88-millimeter flak cannon we just captured. After the gunfights with dozens of Nazi soldiers it took to get here, it's satisfying to watch from a safe distance as the stricken tanks burst into flame.

No, I'm not an actor on the set of a World War II film—but I might as well be. I'm playing Call of Duty 2 on Microsoft's high-powered Xbox 360 gaming console, and I'm in a state of immersion—not just on a sensory level but, surprisingly, on an emotional one, too. It's almost as if I were at the movies.

That verisimilitude is what's most notable about the newest generation of video games. For the better part of a century, the most effective way to envelop an audience and surprise, amuse, sadden, or horrify it has been to make a movie. Everyone who saw Steven Spielberg's 1998 film *Saving Private Ryan*, for example, recalls the first 20 minutes—an unbearably vivid re-creation of the American landing at Omaha Beach on D-Day, filmed largely on handheld cameras to heighten the theatergoer's sense of being present amid the gore and violence. Now imagine that you, not Spielberg, are in charge of the action—deciding where to run and whom to shoot at. That is what it's like to play Call of Duty 2—and that's how close today's games have come to true interactive cinema.

XBOX 360 CORE SYSTEM
Microsoft, $299.99

CALL OF DUTY 2
Activision, $59.99

PROJECT GOTHAM RACING 3
Microsoft Game Studios, $49.99

In fact, I think it's time to scrap the term "video game," which will forever reek of teen-filled arcades and Super Mario Bros., for a coinage more suggestive of the complex character-driven narratives, freely navigable environments, and very nearly photorealistic graphics that now define state-of-the-art titles. I suggest "cinegame." The word acknowledges the grown-up appeal of games like Call of Duty 2—and let's face it, 62 percent of America's roughly 147 million gamers are adults—as well as the fact that the impressive processing power of machines like the Xbox 360 is rapidly pushing these games across the technological boundary between cartoonishness and filmlike veracity.

In days past, no one would have thought of comparing video games to movies. Indeed, the first several generations of games made no attempt at realism. I'm old enough to remember playing Atari's Pong at a friend's house when I was in the third or fourth grade. The beauty of Pong was in its mathematical purity: table tennis reduced to its abstract essence. Of course, that was about all the electronics of the day could do. But as microprocessors have grown in power, game designers have gradually abandoned abstraction in favor of concrete, textured, three-dimensional virtual worlds that can serve as settings for true storytelling. And with the Xbox 360, they've reached an apotheosis.

The machine, which Microsoft launched last November as the successor to the five-year-old Xbox, looks like a typical beige-box PC on the outside. But inside there are three separate CPUs or "cores," each running at 3.2 gigahertz (billions of clock cycles per second), compared to the single two- or three-gigahertz CPU inside the typical PC. That's enough to generate 1,080 lines of resolution, meaning graphics look stunning even on high-definition TVs. All that power makes the Xbox 360 the current king of the video consoles—at least until Sony releases the PlayStation 3 later this year. (The PS3 will feature a new Sony-IBM-Toshiba chip, which will have nine cores and run at more than four gigahertz.)

The Difference

Games for the Xbox 360 are not harder to complete than their predecessors, nor do they require better hand-eye coördination. Indeed, at high speed, Pong is fiendishly difficult. But Xbox 360 games give the player more to look at, think about, and feel.

TIM BOWER

In the case of Call of Duty 2, there's the blood, smoke, and bullets, which strike with an impact you can feel through the Xbox's vibrating controller. There are the moments of pure cinema: a soldier whose gaze follows the bombers flying overhead, a multistory factory that collapses into rubble in a cloud of dust and flame. There is an obsessive level of detail, such as the inlaid wood carvings on an upended desk in a pulverized building. But most of all, there's the continual peril of combat as you and your fellow squad members try to kill Germans before they kill you. As you guide your character through the game's immense 3-D environments, some impressive artificial-intelligence algorithms make your fellow soldiers follow (and sometimes lead), providing covering fire and shouted warnings about snipers and grenades. If you're stupid enough to approach the Germans at close range, you're on your own. But by watching your brothers-in-arms, you can eventually learn how to outmaneuver the enemy—or simply stay hidden.

In fact, though I've watched plenty of World War II movies, I don't think I fully appreciated before playing this game that the most important thing in a soldier's life is finding cover. Nor did I have sufficient understanding of the pandemonium and waste marking the Allied campaigns in Europe and Africa. It may sound trite, but it's true: I think I have a better sense for this war from having played this video game.

As affecting as Call of Duty 2 may be, however, there is another game that shows off the Xbox 360's capabilities even more grandly. It's Project Gotham Racing 3, a Grand Prix–style automobile racing game set on the roads of London, Las Vegas, New York, Tokyo, and Germany's famous Nürburgring. In videoland, objects are constructed from tiny polygons; the more polygons, the smoother and less jagged an object will appear. The designers of PGR3 used up to 105,000 polygons per race car, more than 10 times the number used in Project Gotham Racing 2 for the original Xbox. Add in layer upon layer of effects such as reflections, shadows, dust, and motion blur, and the result is flabbergasting. Replays and still images from PGR3 races are nearly indistinguishable from the real thing *(see www.technologyreview.com/xbox360)*.

I do not mean to argue that realism alone makes a game worth playing or that all games that try to be cinematic are masterpieces. In recent years, it's become common for studios to pepper their games with movielike "cut scenes" in an attempt to wrap human-interest stories around the actual game missions. Rockstar Games, creator of the controversial Grand Theft Auto series, is a leader in this area. Unfortunately, the writing and voice acting in most cut scenes are schlocky. As video game critic Clive Thompson wrote for *Slate* in early 2005,

> These Hollywood flourishes are good for dazzling mainstream journalists and pundits. That's because there's still a weird anxiety about adults playing games. Most people still think that video games are sophomoric kid stuff; the ones that have a narrative and emulate the movies seem more serious and, well, mature. In fact, I think the truth is almost the opposite. The more video games become like movies, the *worse* they are as games.

Thompson would be quite right—if, that is, cut scenes were the only way to give a game sweep and drama. But that's no longer the case. With hardware as fast as Microsoft's, designers can build drama into the missions themselves. Call of Duty 2, for example, has no cut scenes; a few old newsreels suffice to explain the setting for each campaign. Anything more would get in the way, making players into passive lookers-on in a game that's all about lifelike experiences.

Of course, even if I've convinced you that the Xbox 360 is the best thing since the Lumière brothers patented the cinématographe in 1895, you may have trouble buying one. Manufacturing difficulties limited Microsoft's production run to about 600,000 units between the machine's November 22 launch and the end of the holiday season, according to market research firm NPD Group. That wasn't nearly enough to satisfy the enormous demand for consumer electronics; by way of comparison, Apple sold 14 million iPods over the 2005 holidays. Xbox supplies were so low in January, when I was preparing to write this review, that Microsoft itself had run out: an apologetic person at the company's public-relations firm explained to me that it might be several months before a loaner was available. So I resorted to eBay, where I found a man in Corvallis, OR, who was willing to sell his Xbox 360 core system (without accessories such as a hard drive and a second controller) for $499, a mere 60 percent markup over the retail price. Fortunately, production picked up after the holiday season was over, and Microsoft says it expects the shortage to ease by this summer.

Thirty-four years after Pong, video games are finally maturing from arcade-style tests of fine-motor skills into an independent art form. That lag time shouldn't be surprising: it wasn't until 1915, fully 20 years after the invention of motion pictures, that *The Birth of a Nation* set down the basic grammar of movie storytelling, and it was only in 1977, almost 30 years after the birth of network television, that *Roots* introduced the first art form truly unique to TV, the miniseries. Now that video games can credibly evoke emotion and borrow elements from movies and other media without slavishly imitating them, it's time to welcome them into our museums, libraries, and living rooms. TR

Wade Roush is Technology Review*'s executive Web editor.*

PERSONAL TECHNOLOGY

Confessions of a Scan Artist

You, too, can commit your life to digital—and throw away your paper records. By Simson Garfinkel

As our lives become more digitized, a number of eminent computer scientists are starting to warn that our most treasured family photos, heartfelt correspondence, and legal documents might be irretrievably lost if we do not print them on acid-free paper and safely store them in a cool, dark, and dry place. After all, the original Declaration of Independence, written on parchment, is still on display in Washington, DC, but digital documents from even 1990-vintage personal computers can be difficult to read, because few people have five-and-a-half-inch floppy-disk drives anymore.

I think those computer scientists have got it wrong. The problem with paper documents is that they are forever vulnerable to destruction—from fire or flood, for example—because they exist in one place. I prefer electronic documents, which can be easily copied and "backed up" to different locations—different hard drives, different buildings, and even different states. And though it does require dedication to manage your life this way, today's technology makes it easier than ever.

I bought my mother an Apple eMac with a high-speed Internet connection. Every day my family's digital photo album is copied to her computer. Mom gets to see up-to-the-minute photos of her grandchildren, thanks to Apple's marvelous screen saver, and I get reliable off-site backup. Other people I know simply send CD-ROMs to their parents every few months. Either way, the ease of making useful off-site backups demonstrates one of digital documents' real advantages over paper.

FUJITSU SCANSNAP FI-5110EOX2 COLOR DUPLEX SCANNER
$495.00

ABBYY FINEREADER 8.0 PROFESSIONAL
$399.00

ABBYY PDF TRANSFORMER
$49.99

Some of the paper documents that show up at my house, like credit card bills, annual tax statements, and even snapshots from my mother's disposable camera, aren't as easily rendered into digital form, of course. It's all too tempting to throw them into a file cabinet or photo box. Moving them into the digital domain takes work; taking the extra step, and throwing away the paper original, used to require an act of faith. But digital documents are worth the effort, and we should all be creating them. These days, it's relatively easy to understand which formats will survive and be readable in 20 years' time and which are likely to go the way of the eight-track tape.

The key to survival, it turns out, is openness. File formats that are published and can be implemented without payment of a licensing fee—formats, that is, that embody the principles of open-source software—survive, because knowledge about how to read them can be freely incorporated into many applications. Other file formats die when the companies behind them stumble.

Two modern file formats likely to enjoy long-term durability are the Adobe Acrobat portable document format (PDF) and the JPEG image format. That's because both of these formats are public, and there is a wide collection of software compatible with them. Yes, the source code for Acrobat itself is proprietary, but PDF files can be directly opened on the Macintosh platform without the use of any Adobe code. They can also be viewed on Linux machines with an open-source program called GhostScript. JPEG,

meanwhile, is widely used by millions of digital cameras and practically every computer that's sold today. I cannot imagine a future computer system that could not read the JPEG file format. Your digital photos are safe—provided that you have good backups.

So when I get a credit-card or bank statement by mail, I usually go to the organization's website and download a PDF. (I wish these organizations could send the PDFs out by e-mail, but that's another issue.) But many small organizations provide paper statements only. These, like all of my personal papers, I scan with Fujitsu's relatively new ScanSnap FI-5110EOX2. I just load a stack of paper into its hopper and press a button. The ScanSnap scans both sides of your paper at the same time and creates a single PDF file. It knows whether you are scanning a black-and-white or color page and can be programmed to automatically remove blank pages from the final PDF.

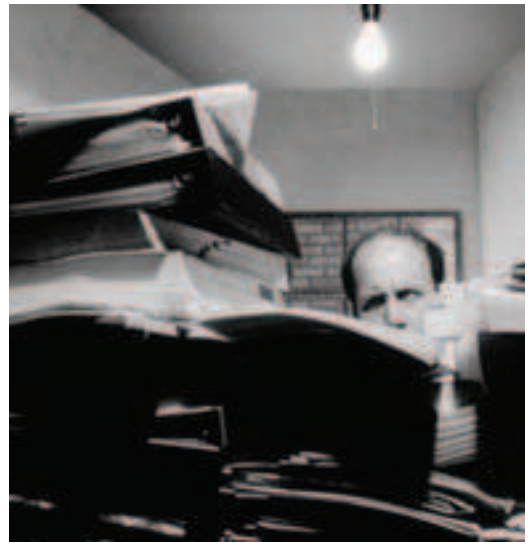
But scanned PDFs are not hassle free. Not only can different PDFs contain different kinds of information, but they can represent it in different ways. Unlike the typical PDF that you might download from a website, the PDF that a scanner produces is an image, not text, so you can't index and search it the way you can, say, a Word document. If you want that added functionality, you need to turn the images back into text. This is done through a technology called optical character recognition (OCR).

Many people think of OCR as clunky technology that frequently makes mistakes. Although that's still true of some OCR engines—most notably, the free engine that ships with some versions of Adobe Acrobat—today's professional OCR engines, like Abbyy Finereader 8.0, can accurately recognize text in a variety of languages, tables of numbers, and even names. As long as you are using Abbyy Finereader 8.0 or comparable software, you'll get good results.

Instead of replacing the original image with the recognized text, which could result in data loss if the recognition software makes any mistakes, modern systems store both versions of a document. This means that you can consult the picture of the paper original but use the text for searching and, if you need to, pasting into other documents.

Today's desktop search engines, like Google Desktop and Apple's Spotlight, can read the text of the PDF files and automatically index them for you. And because PDF is also an open format with many interoperable implementations, there's little chance that you won't be able to read these files in two or three decades.

Personally, I don't like relying on search to find my documents. Instead, I've adopted a file-and-folder system



TOM HUSSEY/THE IMAGE BANK/GETTY

that's remarkably similar to the one I used to use for paper documents in my file cabinets. When I scan a set of paper documents, I give them a descriptive name, like "2005_bank_statements .pdf." I then store this file in a folder named "finance," which I put inside another folder named "2005." This makes it easy to find a document without searching for it. It also makes it easy to back up my important documents to CD-ROM or to another hard drive.

So is there trouble in this electronic paradise? Yes. For starters, the ScanSnap doesn't use the industry-standard interface for digital scanners. For reasons known only to Fujitsu, the scanner can be used only with its proprietary scanning software.

And I've been burned by electronic documents before. Back in the 1990s, I scanned a lot of articles with a low-quality 200-dots-per-inch scanner and stored them in Visioneer's proprietary "Max" format. I'm glad I didn't throw away the originals; recently, I rescanned them all.

But things are different now. Scanners create high-quality images in file formats that are open and widely implemented. For the past two years, I've been scanning my papers and throwing away the originals—and I feel good about doing that. On many occasions I've had to go back and look things up in my digital files. Documents were easier to find, and once I found them, I could send them off by e-mail.

One of the best reasons for committing to digital storage addresses one of the biggest fears people have about it: the question of whether you'll regret, in 20 years, having taken the plunge. If we look at the trend in all of the things that we get and store—correspondence, music, photography—what we see is that more and more of what is coming at us is digital *on arrival*. Do you really expect to get your home heating bill by regular mail in 10 years? Maybe. But by committing to a uniform storage system for all of our personal documents, even if it means, for the moment, having to convert a few hard copies every month to digital files, we are simply giving ourselves a head start on building a single, comprehensive personal library, one whose chief benefit is that it can never burn down. TR

Simson Garfinkel is a postgraduate fellow at Harvard University's Center for Research on Computation and Society.

CHANGES AT NASA

Private Space

Times have never been more promising for proponents of commercial spaceflight. **By Mark Williams**

When the Bush administration announced a new mission for NASA in January 2004, many dismissed it as a cynical P.R. ploy. Yet it was the first time a U.S. administration had declared that the country's policy on manned space exploration was to go into space and keep going *(see "Toward a New Vision of Manned Spaceflight," January 2005)*.

Given that ambition, the "Report of the President's Commission on Implementation of United States Space Exploration Policy"—also dubbed "A Journey to Inspire, Innovate, and Discover"—charted an ostensibly reasonable course. It decreed that when construction on the International Space Station finished in 2010, the shuttle would be mothballed. By 2014, a new manned vehicle—the crew exploration vehicle, or CEV—would make its first flight. Astronauts would take the CEV to the Moon by 2020 and would head for Mars in the following decades. Since the Bush administration gave NASA a limited budget with which to achieve this, some said that the White House wasn't serious; others argued that the tightfistedness was justified, given the agency's history of overruns. In any case, NASA in 2005 announced a design for a four- to six-astronaut CEV resembling the Apollo command module, which would be boosted into space atop a revamped heavy lift vehicle (HLV). NASA's new boss, Michael Griffin, described the combo as "Apollo on steroids."

Because the Bush administration had stipulated that $27 billion of the $104 billion needed for the two vehicles would be freed up only with the shuttle's retirement and the space station's completion in 2010, the president's commission initially called for the first piloted CEV flights for no later than 2014. This would have meant that for four years the official U.S. space program would have had no manned-spaceflight capability, and for eight years taxpayers would have been paying for a program that was doing nothing visibly new. Soon after his appointment, Griffin made clear his displeasure with the plan: "the Apollo spacecraft was brought from contract award to fruition in no more than six years. It seems unacceptable to me that it should take from 2005 to 2014 to do the same thing."

Under Griffin, NASA now plans to deploy the CEV no later than 2012. Moreover, Griffin has broken with NASA tradition. Under his administration, the agency has taken the position that it doesn't make sense to use a costly vehicle like the CEV (at approximately $400 million per flight) to resupply the space station if a cheaper alternative exists. In an October 28, 2005, announcement, "Commercial Orbital Transportation Services (COTS) Space Flight Demonstrations," the agency solicited proposals from companies to build and launch unmanned cargo delivery systems capable of reaching the space station. Once a company achieves that milestone, NASA said, "proposals will also be solicited for…demonstrations [that] will consist of one or more crewed missions to the International Space Station." Ultimately, Griffin envisions NASA not just purchasing rockets to carry crew and cargo from commercial firms but even buying propellant from commercially operated fuel stations in Earth orbit.

"COMMERCIAL ORBITAL TRANSPORTATION SERVICES (COTS) SPACE FLIGHT DEMONSTRATIONS"
Solicitation number: JSC-COTS-1
Posted: October 28, 2005
Contracting office: NASA/ Lyndon B. Johnson Space Center

RETURN TO THE MOON: EXPLORATION, ENTERPRISE, AND ENERGY IN THE HUMAN SETTLEMENT OF SPACE
By Harrison H. Schmitt
Springer, 2005, $25.00

Fighting Gravity

Griffin won't have an easy time. It has been 33 years since the last humans, *Apollo 17*'s Harrison Schmitt and Eugene Cernan, walked on the Moon. The public presumption during the Apollo years that manned exploration of our solar system was inevitable has given way to the perception that human spaceflight is too hard, dangerous, and expensive. Exploration, the new orthodoxy runs, belongs to unmanned probes sailing through deep space and robots crawling over planets.

Still, though the rationalists are right to argue that the short-term scientific payoffs will come from unmanned exploration, the effort to go into space has always been about more than science. National pride, competition for technological supremacy, the thrill of exploration, and hopes for humankind's advancement have all played their part. In 2006, moreover, technological progress has improved the prospect that manned, commercial flights into space can be economical and perhaps even profitable.

Richard Branson's Virgin Galactic, for instance, claims to have 42,000 customers registered for $200,000 rides to the edge of space, indicating significant public support and consumer demand. Sending tourists up for five to seven minutes of weightlessness, however, isn't manned spaceflight.

Among the small, young aerospace companies that have proposed plans to send human-sized payloads into orbit, including t/Space, SpaceDev, and Interorbital Systems, Elon Musk's SpaceX is often touted as a frontrunner. Musk is an entrepreneur who cofounded PayPal, the online-payment

service, and SpaceX has actually built prototype rockets, unlike many of its competitors. The company has made bold promises and adopted aggressive business tactics, filing suit in 2005 against Boeing and Lockheed Martin, both of which it accused of violating antitrust laws and inhibiting competition. But SpaceX had to scrub the first test launches of its rocket, the Falcon 1, which is designed to loft small, satellite-sized payloads into orbit and constitutes a feasibility study for the future development of larger launchers for human cargoes.

NASA's initial efforts to get off the ground saw worse failures. But at the outset, anyway, NASA's entire reason for being was that the U.S. government believed that a successful space program was essential to America's security and standing. Things have changed. Musk and other entrepreneurs are left to appeal not to our patriotism but to our pocketbooks: they claim that their companies can make manned launches far less expensive than either NASA missions or today's main alternative, launches using the Russian company Energia's Zenit rockets.

PETER FOLEY/EPA/CORBIS

Virgin Galactic's Richard Branson wants to sell you a $200,000 ticket to ride.

Some proposals from private companies represent transformational thinking about manned spaceflight's economics. In an article for the Mars Society, of which he is president, Robert Zubrin suggests an alternative approach for NASA's return to the Moon, with a CEV that carries three or four crew members, not four to six. Zubrin, an aerospace engineer formerly with Lockheed and founder of the aerospace company Pioneer Astronautics, argues that this smaller, lighter spacecraft could carry enough fuel to reach the Moon, enter orbit, land, and return to Earth *without* a separate landing module or an Apollo-style rendezvous in lunar orbit. Such a craft would be simpler and cheaper to build.

NASA could even propose, Zubrin suggests, that companies compete for the CEV contract. And the money NASA saved by ordering a smaller CEV, Zubrin writes, could be immediately applied to the development of the heavy lift vehicle. The CEV and the HLV could therefore be completed sooner, allowing the shuttle's early retirement, saving even more money.

Others have their own scenarios for returning to the Moon on the cheap; Poway, CA–based SpaceDev, for example, proposes placing a series of habitat modules in lunar orbit and on the surface and sending down one astronaut at a time on a personal "rocket chair." It claims that 40 people could visit the Moon in this way "for the cost of NASA's first mission."

Apollo 17 astronaut Harrison Schmitt, a trained geologist, believes that there's a highly practical reason for going back to the Moon: solar wind impregnates the lunar dust with a nonradioactive isotope called helium-3, which could be useful as a fuel for large-scale nuclear fusion. Schmitt has just published a book, *Return to the Moon: Exploration, Enterprise, and Energy in the Human Settlement of Space*, which recognizes that any permanent return to the Moon is unlikely in the absence of help from private enterprise.

Schmitt's futuristic scheme, of course, entails sending significant quantities of lunar dust to Earth for processing, but he calls that "a relatively small challenge" compared to developing fusion plants and lunar mining facilities. He suggests options for powering transport craft—including rocket boosters and electromagnetism—that would make use of lunar resources.

Indeed, escaping the Moon's weak gravity is comparatively easy; the hardest part of space travel is getting from Earth's surface into orbit. From there, a spacecraft can go anywhere in the solar system for roughly the same amount of energy. So once we reach a point where commercial enterprises can supply cheap, reliable means to reach orbit, much more will become possible.

Under Griffin's leadership, NASA seems likely to underwrite part of this effort—as well it should. If the agency hopes to send more Americans into space within the Bush administration's budget, it will need to tap into new ideas from the commercial realm—where money *is* an object. TR

Mark Williams is a contributing writer at Technology Review.

A Better Toxicity Test

MIT's Sangeeta Bhatia demonstrates how to grow miniature liver tissues in the lab. By Katherine Bourzac

Sitting at a computer connected to a large microscope, Salman Khetani calls up a kaleidoscopic image: green islands of human liver cells in a hexagonal pattern, surrounded by a red sea of support cells. Sangeeta Bhatia, Khetani's advisor, says that the cells have been carefully patterned to hit the liver "sweet spot." Arranged just so—in 37 colonies about 1,200 micrometers from each other—the cells behave as though they were in the human body.

When grown in the lab using existing methods, liver cells can survive for a day or two, but over the course of a week, they lose the ability to perform their liver-specific functions and then die. Bhatia and Khetani's cells, on the other hand, function for about a month. They secrete the blood protein albumin, synthesize urea, and make the enzymes necessary to break down drugs and toxins. Bhatia believes that the cells act enough like human tissue that they could be used to screen new drugs for liver toxicity or to study metabolism and, possibly, hepatitis C, a virus that grows only in human tissue. Indeed, the researchers have already developed a drug toxicity test that uses liver cells arranged in their signature hexagonal pattern.

In addition to being a major health problem, liver toxicity is the primary reason pharmaceutical companies recall existing drugs or abandon new ones that are under development. Bhatia says that's because "when you're developing new [drugs], there aren't really good models of human liver." Instead, drug companies rely on cancer cells, dying liver cells, or rat tissue—poor substitutes for fully functioning human liver tissue. Bhatia and Khetani believe they can supply a better model.

The Breakthrough

Bhatia, an associate professor in the Department of Health Sciences and Technology and the Department of Electrical Engineering and Computer Science at MIT, developed her patterning technique using rat cells, when she was in graduate school in the mid-1990s. At the time, she was interested in using micropatterning, an emerging technique for physically arranging cells in culture, to build a dialysis-like device to support patients with liver disease. For her PhD, Bhatia worked on using the technique to bolster cell function and was particularly interested in finicky cells like liver cells (also called hepatocytes).

Inspired by the work of others in her lab who were growing multiple cell types in the same cultures and combining fibroblasts—supportive cells that normally live in connective tissue—with skin cells, she tried micropatterning fibroblasts alongside her hepatocytes. Micropatterning more than one cell type at a time and regulating the interaction that hepatocytes had with each other, and with the secondary cells, was an innovation. The fibroblasts Bhatia borrowed for her experiments turned out to be particularly good at bolstering liver functions. She describes her breakthrough as "a happy, lucky thing that I just stumbled upon."

Even though there are no fibroblasts in the human liver, their presence in Bhatia's cultures coddles the hepatocytes and keeps them functioning. Part of the reason that cells behave like liver, lung, or muscle cells is their environment: signals from neighboring cells, physical forces, and the matrix of supportive proteins stabilizing them. As successful as the method has proven to be, Bhatia is still investigating what exactly causes each patterned hepatocyte island to behave like liver tissue.

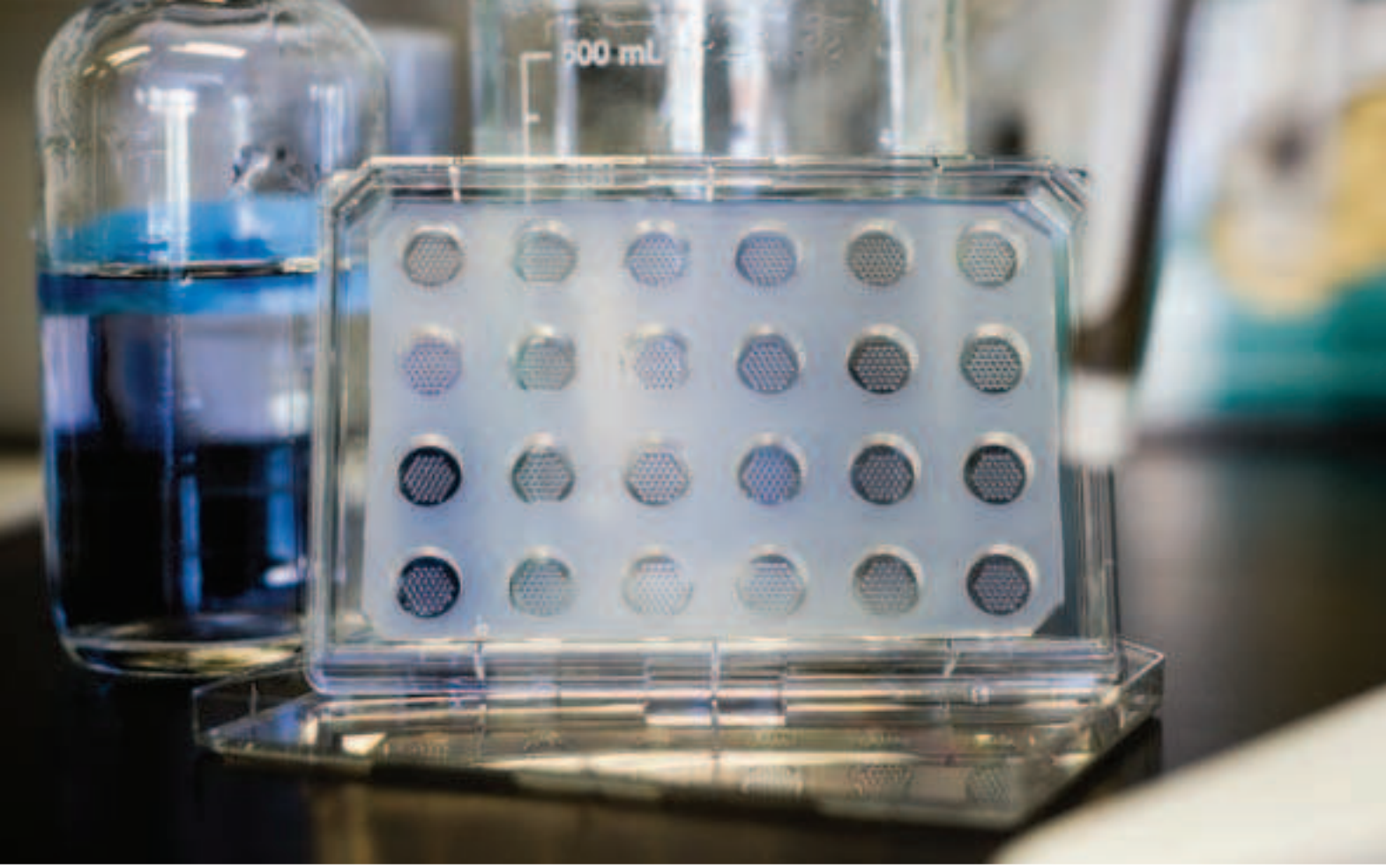
For his PhD, Khetani, now a postdoc at MIT, was able to apply Bhatia's technique to human hepatocytes, making possible the development of the toxicity test. Bhatia says Khetani's work "was a logical extension of mine, but again surprisingly, human hepatocytes turned out to be even more sensitive to clustering than rat hepatocytes."

Others have attempted to grow functioning liver tissues on scaffolds. But, says Khetani, this approach lets the cells do their own organizing, so the architecture of the resulting models is different every time. Bhatia and Khetani, by contrast, precisely specify the organization of the cells in their model, giving them tighter control over functionality.

To verify that their micropatterned liver cells actually behave like hepatocytes in the human body, Bhatia and Khetani put them through a series of rigorous tests. They analyzed the cells' gene-expression profile and measured the amount of drug-metabolizing enzymes they produced. They exposed the cells to a battery of substances known to be either benign or toxic to the human liver, from caffeine to cadmium. To test the toxicity of a drug, Khetani creates a solution of the desired concentration and pipettes it into a set of wells, where it's incubated with the liver tissues. Then he looks for changes in hepatocyte function or cell death.

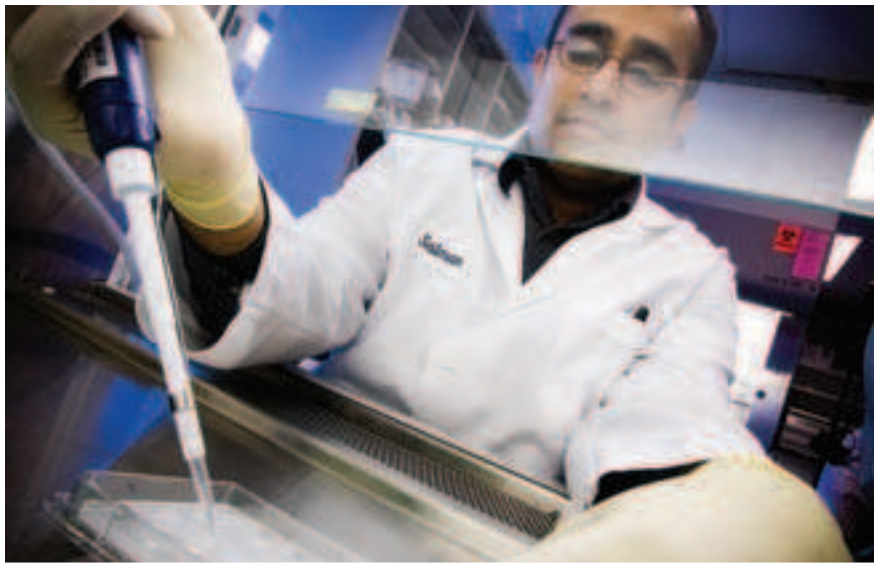
Drug companies could, says Bhatia, use this assay to compare several chemically similar compounds and eliminate toxic ones early in the drug development process. "If I were at a drug company," she asks, "and my medicinal chemists gave me four compounds, could I have picked which one would have been the most toxic using my assay?" The answer seems to be yes. She and Khetani have compared chemically similar drugs known to be benign or toxic to the liver and confirmed that the new assay can measure differences in toxicity.

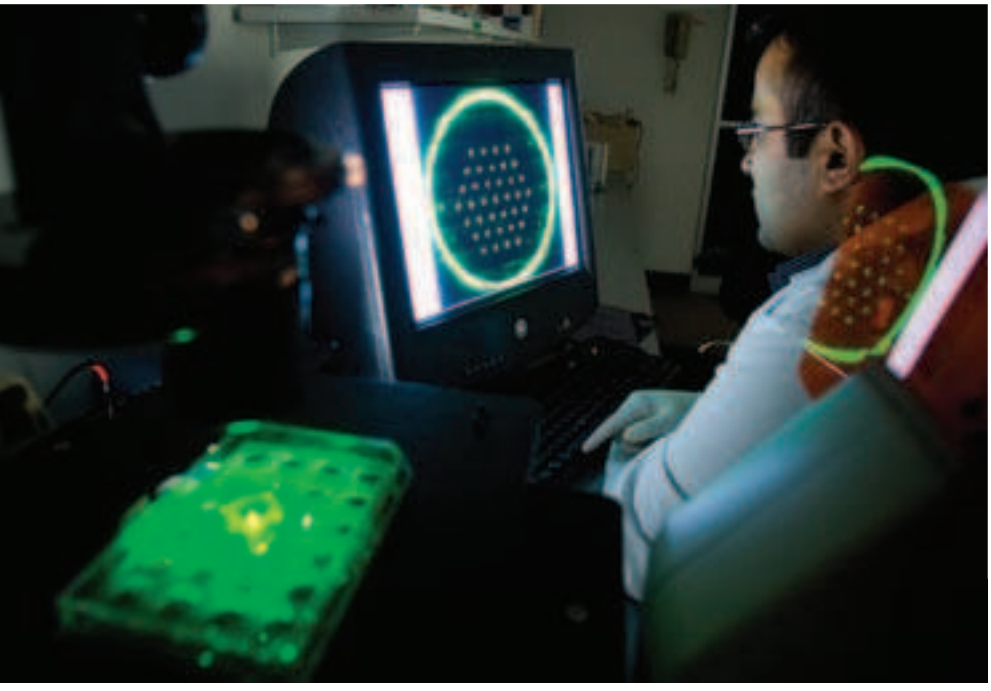
PHOTOGRAPHS BY PORTER GIFFORD

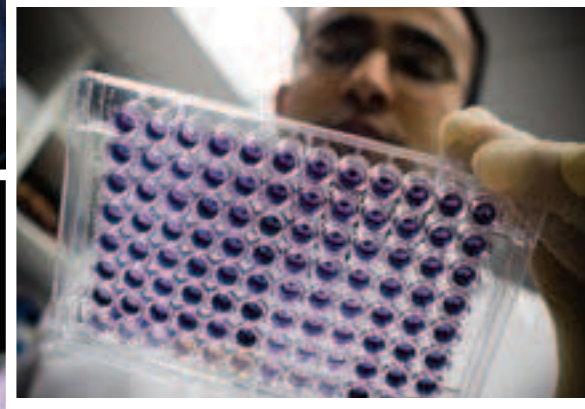


LIVER IN A WELL

MIT's Sangeeta Bhatia (left) grows and tests liver cells on a rectangular plastic plate (top). A thick layer of a rubbery material (PDMS) with holes in it adheres to the plastic plate to create 24 wells. At the bottom of each well is a stencil made of the same material, with 37 tiny round holes arranged in a hexagon. The small stencils are molded on a silicon disc similar to the one pictured above. The silicon mold is created using photolithography, the same technique used to make computer chips. Collagen is poured over the stencils; it falls through the holes in a hexagonal pattern. When the collagen dries, the stencils are peeled away.







COLORFUL TEST

Salman Khetani pipettes collagen onto the stencils (left), then seeds the wells with liver cells. The liver cells gather atop the collagen circles because they cannot adhere to the plastic of the plate. After they've settled, Khetani pipettes support cells into the wells. The entire process takes between several hours and a day. Under a fluorescent microscope (bottom), the liver cells in a single well glow green. After liver cells and a drug are incubated together, Khetani tests the cells' viability. The purple color (below) indicates cell activity.

Strengths and Limitations

Bhatia's assay is good at detecting drugs toxic to the general population, but it may not uncover drugs with adverse effects on only a small number of people. It might not, that is, have detected the trouble with Rezulin, a diabetes drug that caused liver damage in many patients and which the U.S. Food and Drug Administration ordered off the market in 2000. The liver cells in the assays do not represent a wide enough sample of the population to predict such effects, though it's theoretically possible to test a drug on cells from thousands of different livers.

The assay is unique in being able to test drugs for chronic toxicity, which is caused by low-level repeat exposure, "which is actually the way we take our drugs clinically," says Bhatia—one pill a day. Bhatia's model could be used to test the effects of a drug over four to six weeks. Existing models simply cannot detect chronic effects because liver cells die so quickly in culture. Bhatia says that pharmaceutical companies know that potential drugs that become toxic only over time are slipping through the cracks, but the FDA does not require chronic toxicity tests. "We're in this kind of funny position where we've developed a really powerful tool and have to convince people to use it."

The miniature tissues can also be used to detect acute toxicity, which has much more immediate effects. Acute toxicity can be studied using an existing method, with simple cultures of hepatocytes that die within a week. But Bhatia believes that her assay will be more efficient: because it uses wells, it requires a lower volume of drugs, and the micropatterning means fewer hepatocytes are required.

Bhatia is developing her test for commercialization, and several pharmaceutical companies are interested. She and Khetani are also looking into other uses for the assay—for example, studying interactions between drugs and how liver cells transport drugs. "My hope is that the assay would make drugs safer, better labeled, and would help ensure that toxic drugs never reach patients," says Bhatia. TR

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Toyota Prius

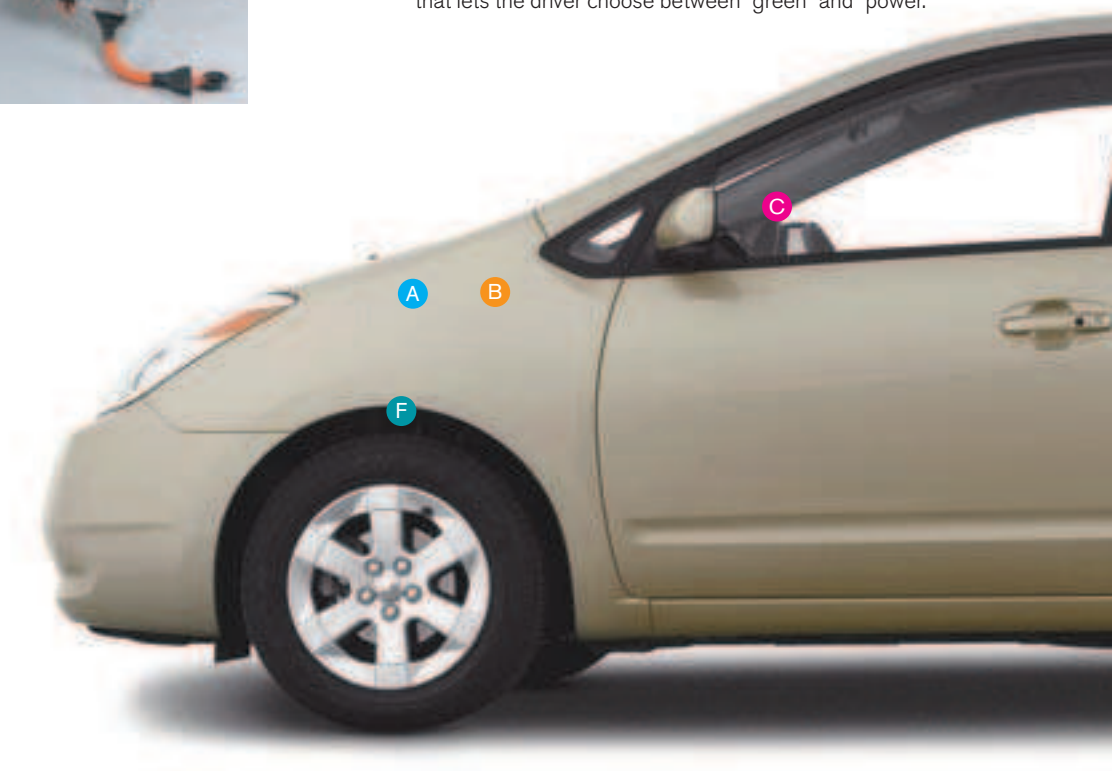
The Prius, now in its fifth year on the North American market and its third design, is the world's best-selling gas-electric hybrid car. Its success derives largely from the clever technologies described here. By Daniel Turner

A Hybrid Power Plant

Toyota calls its gas engine–electric motor combination a "hybrid synergy drive." The Prius mates a 76-horsepower, 1.5-liter, four-cylinder engine with a 67-horsepower electric motor to deliver about 55 miles per gallon. Yet it can also zip from zero to 60 miles per hour in around 10 seconds. The engine uses the Atkinson-Miller high-expansion principle, closing its intake valves late in the compression cycle. This gets more power out of less fuel but gives less low-end torque. Atkinson-Miller engines are therefore perfect for hybrids like the Prius, whose standing starts are powered by the electric motor. In fact, the Prius's engine doesn't even turn on initially; the motor gets the car around town at low speeds. On the highway, the Prius's engine takes over and also recharges the battery. When you stop at a tollbooth, the engine shuts off, and the car falls silent, which can be disconcerting for drivers new to the car.

C Interior

The vehicle information system, an LCD screen on the dashboard, displays mileage data and a graphic showing whether the electric motor or gas engine—or both—is on. That seems to have inspired hackers. CalCars.org, a Palo Alto, CA–based group of engineers and entrepreneurs who love low-carbon technologies, has customized a Prius with extra battery packs and an electrical plug that fits into a wall outlet; the modified Prius reduces use of the gas engine through a software hack that fools the hybrid control system. European Priuses have an "electric only" button, and according to the *Wall Street Journal*, Toyota is considering including a switch in future models that lets the driver choose between "green" and "power."



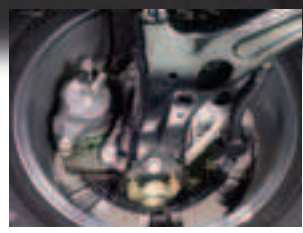
B Transmission

A continuously variable transmission (CVT) provides a continuous range of gear ratios, rather than the discrete steps of manual and automatic transmissions. However, CVTs based on the traditional two-pulley-and-a-belt system, first used in automobiles in the 1950s, often fail, because the belts cannot withstand the stress of high-horsepower engines. The Prius's CVT gets around this problem by using a planetary gear system, which offers greater reliability. The driver experiences the same benefits that previous CVT designs offered: instead of the usual "stair-step" engine noise, you'll hear a smooth, rising hum as the Prius comes up to speed.

PRIUS: SAM LIM/TRANSTOCK; INSET PHOTOS COURTESY OF TOYOTA

D Frame

No matter how efficient its power plant, the Prius wouldn't get good mileage if it had the aerodynamics of a brick. As professional cyclists know, most of a vehicle's propulsive energy is lost to air resistance. Buckminster Fuller recognized this fact when he designed his egg-shaped Dymaxion car in the 1930s. Toyota claims a drag coefficient of .26 for the Prius (for many SUVs, it's more than .35), thanks in part to low-profile tires, spats around the front wheels to reduce trailing turbulence, a chin spoiler, the overall rounded shape, and other small features such as plastic trim rings around the alloy hubcaps. One of the few production cars that beat this drag coefficient is the hybrid Honda Insight, which comes in at a reported .25.



F Regenerative Brakes

The gas engine isn't the only way a Prius recharges its battery. Every time you hit the brakes, some of the kinetic energy that usually generates heat is captured and reused. When the brakes are activated, the wheels engage a differential-like power splitter, which acts as a generator connected to the electric motor; the generator creates AC power, which is sent through an inverter and transformed to DC current, which charges the battery. Previous gas-powered cars had no need for, and no place to store, the electric charge such brakes generate.

E Battery

The Prius uses a nickel–metal hydride battery, composed of an electrolyte gel between cell plates, all sealed in a plastic case. The casing helps prevent battery leakage, even in case of collision. A few more safety notes: while the battery puts out more than 200 volts—a potentially lethal shock—the high-voltage system is automatically disabled at impact, even before the car's air bags are deployed, and all high-voltage wiring is colored bright orange to identify it. Toyota warranties the battery for eight years or 100,000 miles (longer in California) and claims that the current $3,000 replacement cost should fall in the years ahead. In addition, Toyota claims it recycles much of the material from used Prius batteries.

G Emissions

The Prius meets two emissions standards: the Super Ultra-Low Emissions Vehicle standard and the Advanced Technology Partial Zero Emissions Vehicle standard. The Prius's clean running is partly due to reduced gasoline use and the high-compression engine, but Toyota has also engineered a few clever tricks. One is a thermos-like bottle used to keep engine coolant at the correct temperature while the car is in use; the bottle keeps the engine warm when it isn't running, eliminating the extra pollution created when a cold (and therefore inefficient) engine starts up. Toyota claims that the Prius generates 80 percent less smog-forming emissions than the average new vehicle. Then again, a lot of new vehicles are gas-guzzling SUVs.

An Age-Old Problem

Predictions about gerontology made almost a lifetime ago still hold true today.

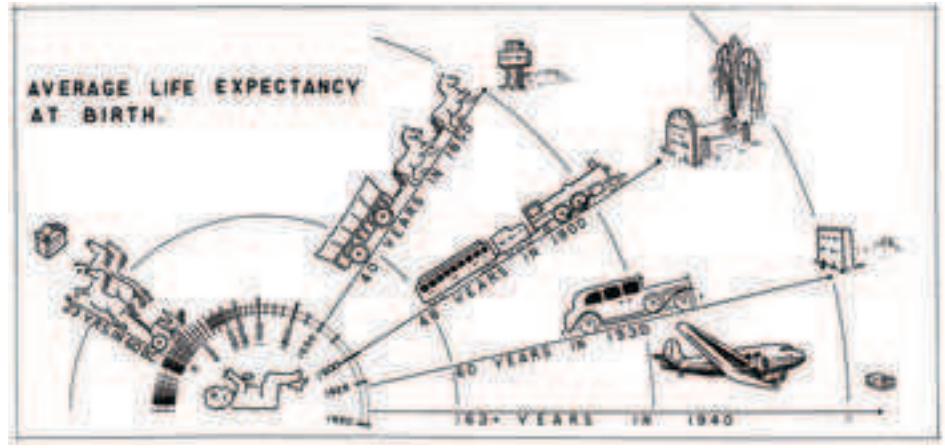
By Jessica B. Baker

Americans today may be more concerned with living longer than at any point in their history. But the science of aging is by no means young. As molecular biologists begin to understand the mechanisms behind the aging process *(see "The Fountain of Health," p. 72)*, they address questions raised in the pages of this magazine 65 years ago. In the June 1941 issue of *Technology Review*, Edward J. Stieglitz urged the scientific community to pursue gerontology. Noting the dramatic increase in life expectancy over the first part of the 20th century, he wrote,

…in 1900 only 17 per cent of the total population of the United States were forty-five years old or more. In 1940, 26.5 per cent were over forty-five, and conservative projection results in the estimate that in 1980—only forty years hence—more than 40 per cent of our population will be over forty-five years of age.

Figures from the 1940 census reveal that the median age of the population of this country increased from 26.4 years in 1930 to 28.9 years in 1940. This is an increase of two and a half years of median age within a decade. The median age of the population will probably be forty-four years in another half century.… Such figures speak for themselves. Because of them, gerontology, the science of aging is no longer merely academically interesting but has become an urgent matter in the minds of those who can see the handwriting on the wall.

As it turns out, those conservative estimates were wrong. In 1980, only 31.1 percent of the population was 45 or older, and in 1990, the median age merely reached 32.3 years, an increase of 3.4 years—not the predicted 15.1—over 50 years. We can't fault Stieglitz for his exuberance. As he looked back at the dramatic historic increases in average life expectancy—from 23 years in ancient Rome to 40 years for a New Englander in 1850, and up to 63 years for his contemporaries almost a century later—Stieglitz expected to see continued robust improvements in longevity. Not only did Stieglitz presciently argue for advancements in gerontology, he raised questions about the biology of aging that precisely—and amazingly—echo those posed by scientists today.



(1) The biology of senescence as a process. *Here our ignorance is profound. Unanswered as yet are such fundamental questions as: Just what happens to a cell with aging? Why does aging occur? What accelerates or retards it? What mechanisms are involved? Why? The elucidation of these basic questions may solve many riddles—among them the riddle of cancer and perhaps that of arteriosclerosis. Scientifically, the cancer problem is but a subdivision of the bigger question of aging.*

(2) The clinical problems of senescence in man. *These questions are clearly divisible into those relating to normal senescence and those relating to abnormality due to disorders associated with advancing years…. Chronologic age, as measured in years and months, is not identical with biologic age. Physiologic age varies with each individual. The greater the duration of life, the greater the variation. Furthermore, no individual ages uniformly throughout, for different structures and systems age at different rates at various times in the life span….*

(3) Socio-economic problems. *The sociologic problems introduced by increased longevity, greater life expectancy, and the rising median age of the population are immense and extremely complex. Industry is just awakening to the implications of the fact that the average age of employees is increasing at a surprising rate. Problems of placement and retirement, utilization and conservation of the health of older men in positions of greater responsibility, the complexities of workmen's compensation laws in relation to occupational exacerbation of pre-existent disease, and many more questions are becoming increasingly urgent.* TR

MARTIN ROSSE

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